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PAEDIATRIC SURGERY · Fourth Edition

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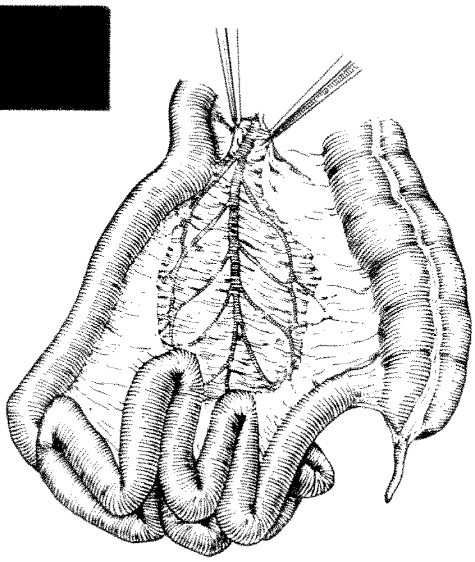

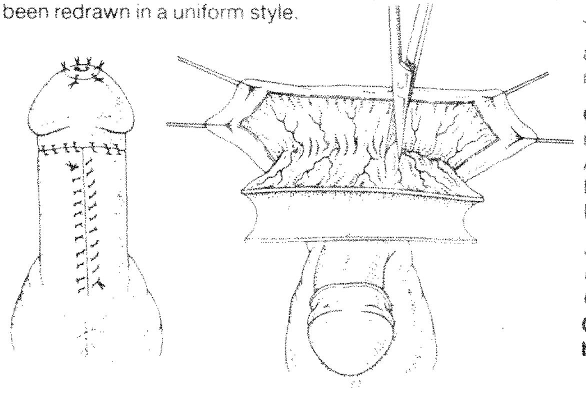

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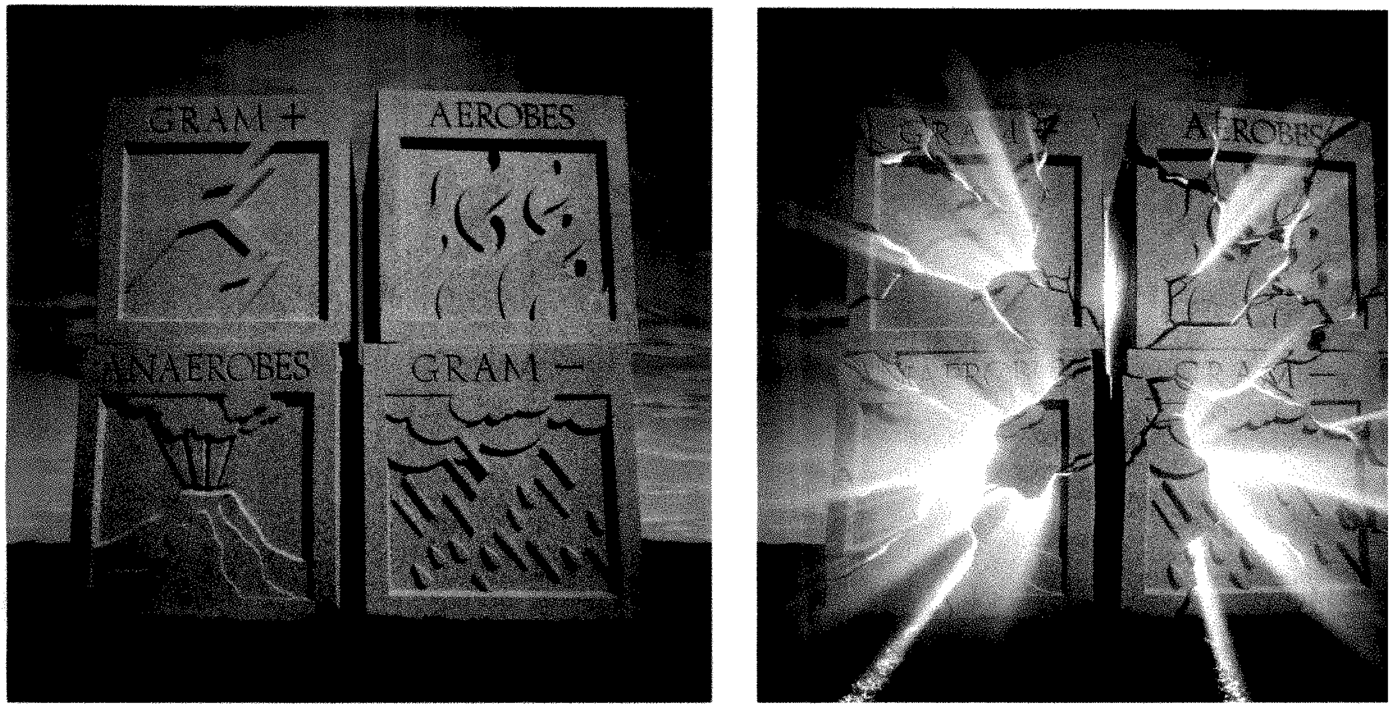

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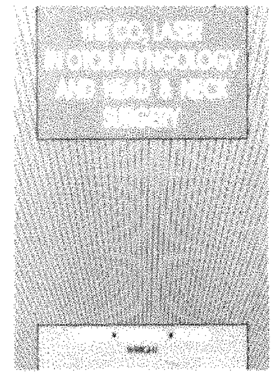

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Br. J. Surg. 1988, Vol. 75, November, 1049–1050

Red alert

In 1907 Bashford *et al.*[1] showed that allogeneic blood transfusions diminished solid tumour growth in mice. In 1955 Snell *et al.*[2] found that the mortality from sarcoma growth was zero in untransfused ASW mice, but 96 per cent of transfused mice died of disseminated tumour. In 1981 growth of a chemically induced MC7 sarcoma in the rat was shown to be significantly enhanced following allogeneic blood transfusion[3]. Plasma suppressive activity was also enhanced, while lymphocyte responsiveness to purified protein derivative of *Myobacterium tuberculosis* and phytohaemagglutinin maximally diminished up to 30 days but lasted significantly longer[4]. Jeekel's group[5] published conflicting results using two different tumours in the Brown Norway rat. Third-party blood caused a reduction in lung metastases from a highly immunogenic radiation-induced basal cell carcinoma and reduced subcutaneous growth of a less immunogenic chemically-induced duodenal adenocarcinoma. Horimi *et al.*[6] investigated which component of the transfusion might be responsible for accelerating growth in their MH134 murine hepatoma model. Tumour growth was accelerated after a single transfusion of allogeneic whole blood but not by erythrocyte transfusions. In a different strain combination-tumour growth was enhanced by transfusion of third-party plasma, thymic cells, or peripheral T lymphocytes, but erythrocytes alone failed to augment growth. This finding was confirmed in the Lewis lung cancer model[7]. Rossler *et al.*[8] published a series of experiments involving five different tumours. Third-party blood had no effect on tumour growth even though 20 transfusions of 1·0 ml were given. Further reports indicated that blood transfusions had no effect on tumour take, growth or induction rates. Despite the lack of effect on tumour growth, the animals showed evidence of depressed cell-mediated immunity. Blood transfusion had no effect on peripheral blood lymphocyte subsets[9,10]. Judson *et al.*[11] examined the effect of transfusion on the growth of the RIII breast tumour in mice and failed to show any difference between the syngeneic and allogeneic groups. By 1986 Jeekel *et al.*[12], using the LS175 non-immunogenic sarcoma in the rat, had shown that transfusion 7 days before tumour inoculation had no effect on the establishment of lung metastases, but if the transfusion was given 7 days after tumour passage then growth of the established secondaries was accelerated. In the highly immunogenic BC1618 basal cell carcinoma, blood transfusion inhibited the formation of metastases only if given before tumour cells. More recently, the MC7 sarcoma model used by Francis *et al.* was examined in more detail. Transfusion of third-party blood appears to augment tumour growth in a dose-dependent manner, may be synergistic with the immunosuppression of surgery, and is maximal when plasma-free washed cells (erythrocytes and all leucocytes) are transfused (N. R. Parrott, T. W. J. Lennard, G. Proud *et al.*, unpublished results).

A number of papers have appeared recently, some showing accelerated tumour growth and some showing no effect in transfused cancer patients. Parrott *et al.*[13] showed that cancer recurrence was greater in a series of 517 patients with colorectal cancer if they had received blood transfusion. Other smaller series have confirmed this association[14,15] and Blumberg *et al.*[15] found a 34 per cent survival advantage in non-transfused patients. However, enhanced tumour growth in transfused patients is not a universal finding[16–18]. Francis and Judson[19] showed a significant effect of transfusion during operation but no effect with other perioperative transfusions, thus raising the question of whether blood transfusion is merely a marker for the biologically more aggressive tumour. All the studies with one exception[20] refer only to blood transfusion, yet it is well known that the substance provided as 'blood' may be anything from whole blood to plasma-reduced or packed red cells. Furthermore, fresh whole allogeneic blood with viable white cells elicits a more vigorous immune response than stored blood[21].

Sufficient evidence exists to raise considerable suspicion that blood transfusion could be damaging some patients with cancer. Traditional surgical practice demands that pre-operative anaemia and even modest operative blood losses are treated by transfusion, which may be quite the wrong thing to do. Prospective studies are needed urgently and should take account of past transfusion history and perioperative transfusion, including precise details of the time of transfusion and composition of the blood used. The ideal trial would randomize patients with potentially curable neoplasms to receive blood or not. This would require some individuals to be transfused who might not require blood. They would then be subjected to two risks: the small risks of transfusion in general (e.g. non-A, non-B hepatitis), and the

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hypothetical risks raised by transfusion studies in cancer. It is by such prejudices and prejudgements that science is stifled but the ethics of a deliberate transfusion study would trouble many of us.

A number of prospective trials have been proposed but few address the fundamental question of whether third-party transfusion enhances the risk of cancer recurrence. Many ask which aspect of the transfusion is causing increased risk of metastases and this prejudges the issue. Prospective studies can be done in a way that would not give blood to individuals who did not require it on clinical grounds. Each study should be confined to patients with one form of cancer, and should only include patients receiving potentially curative surgery. Patients who did not require blood transfusion would not be included. The majority of patients who need transfusion require three units of blood or less. It is possible and ethical to randomize them to receive either whole blood or blood substitutes. Alternatively, the question could be answered by randomizing to autotransfusion or third-party blood, as Jeekel and his colleagues are doing. A multicentre study done in either way could resolve the dilemma in 5 years and if there were a real transfusion effect the next stage would be to examine which component of the transfusion was responsible.

Meanwhile it is possible that we are doing a grave disservice to our cancer patients when we transfuse them for indications that are less than absolute. What should we do while awaiting the outcome of clinical trials? For ourselves, unless life-threatening haemorrhage dictated otherwise, we would choose not to have a perioperative transfusion while undergoing cancer surgery. We would prefer to go home a little anaemic, with our iron tablets, and perhaps still be around free from recurrence to see the outcome of prospective trials in 5 years time.

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Br. J. Surg. 1988, Vol. 75, November, 1051–1052

Percutaneous transluminal angioplasty and vascular surgery for lower limb ischaemia

Any technique for combating disease which is, relatively, fast, cheap, effective and free from side effects demands attention and these are the features which have established a place for percutaneous transluminal angioplasty (PTA) in the management of arterial occlusive disease affecting the lower limbs. That PTA can be performed quickly, often requiring no more than a 24 h hospital stay, is self-evident, and in some centres it is even now performed on an outpatient basis. Speed is the main reason for the costs of PTA being only about one-quarter of those of reconstructive vascular surgery, such as aortofemoral or femoropopliteal bypass. It has been estimated that, in the USA, PTA could be used as the initial form of treatment for up to 40 per cent of patients needing intervention for peripheral vascular disease and that such a policy, as opposed to surgery only, would result in an annual saving not only of $82 million but, more importantly, of 352 lives and 5006 limbs with patent vessels[1].

Cost efficiency is possible because the technique works. This was not readily accepted 10 years ago by sceptical vascular surgeons, who were more used to endarteriectomy and bypass grafting and found it difficult to believe that mechanical over-distension of diseased arteries could produce long-term patency. Fair criticism of the early studies of PTA was made on the grounds of inadequate objectivity and uniformity in the evaluation of outcome. Furthermore, the selection of patients, who often had quite limited lesions, also made it difficult to compare PTA with most surgical series which dealt with a wider spectrum of disease. It is only with further development and study of the results of PTA that its worth has become clear. Five-year patencies after angioplasty of 80–90 per cent for iliac lesions and of 60–70 per cent for (superficial) femoral artery lesions have been reported[2–4], although some caution is needed when interpreting these excellent results. Even in modern angioplasty series there are still high proportions of patients with favourable lesions (especially in terms of short length of stenosis or absence of occlusion) and these patients are likely to form a privileged group in terms of outcome no matter what treatment is used to overcome their disease. It should also be remembered that the best results for angioplasty are obtained by ignoring a 4–23 per cent technical failure rate. Nevertheless, it cannot be denied that for limited disease the technique is a proven major therapeutic advance.

Initial worries about the safety of PTA have also been overcome with increasing experience. Although a wide range of complication rates (of up to 44 per cent) have been reported, most complications are minor problems like haematomata. Thrombosis, vessel perforation and embolism are rare, and in most series complications requiring surgical intervention affect less than 5 per cent of patients. Such intervention is usually able not only to correct the complication of PTA but also to bypass the affected segment of artery for which angioplasty was performed in the first place.

The principal factor responsible for the wide range of reported complication rates is the variation in indication for PTA. When this is undertaken in short segment lesions in (usually) claudicants, complications tend to be rare. On the other hand, when angioplasty is done for severe disease, often for limb salvage in the elderly, complications are more frequent. Yet the technique has much to offer the debilitated patient for whom the risk of surgery may be higher still. PTA, therefore, has its major role at the extremes of vascular disease. On the one hand it may be used in early, short segment disease in relatively fit people, while on the other it may be used in the debilitated patient with critical ischaemia. In both circumstances patients may be treated who would not otherwise have been offered operation.

The larger middle ground has so far been left to vascular surgery, although PTA continues to encroach here and may make further inroads if recanalization devices (laser assisted angioplasty, transluminal atherectomy or rotational thrombectomy) and intravascular mechanical support by endoprostheses fulfil their early promise[5,6]. While angioplasty may diminish the need for vascular surgery in some areas, it also holds the exciting prospect of increasing our surgical capability in others. Preoperative and peroperative angioplasty can both be used to increase run-in and run-off for a vascular graft. The common situations are iliac artery dilatation to augment

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run-in for femorofemoral or femoropopliteal bypass, and superficial femoral artery dilatation to increase run-off for aortofemoral bypass[7]. When the peroperative option is used it is likely to be the vascular surgeon rather than the radiologist who wields the balloon catheter. Finally, angioplasty may also be of direct benefit in surgical patients when it is used to treat reconstructive complications, especially stenoses in vein bypass grafts[8].

PTA has been a significant advance in the management of occlusive disease affecting the lower limbs. The grey areas at both extremes of disease which may be treated by either PTA or vascular surgery require close co-operation between the vascular surgeon and the radiologist. Surgical salvage of angioplasty complications likewise demands this co-operation as does pre- and peroperative angioplasty. The best results of intervention for vascular disease are likely to be obtained in those hospitals where vascular surgeons and interventional radiologists maintain close links and strive to achieve an understanding of the benefits and drawbacks of both disciplines.

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Thrombosis prophylaxis with low molecular weight heparin in total hip replacement

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In a randomized prospective trial, the efficacy of low molecular weight heparin (LMWH) (Fragmin®) and dextran 70 (Macrodex®) in preventing deep vein thrombosis (DVT) in the legs was evaluated in 98 consecutive patients undergoing elective total hip replacement. The patients were randomly allocated to receive either 2500 anti-factor Xa units LMWH twice daily for 7 days, with the first dose given 2 h before surgery; or 500 ml dextran 70 twice during the day of operation, followed by a single infusion of 500 ml on the first and again on the third postoperative day. DVT was assessed by ^{125}I-fibrinogen test for 2 weeks postoperatively, a positive test being followed by phlebography. DVT developed in 22 (45 per cent) of 49 patients receiving dextran 70 and in 10 (20 per cent) of 49 patients in the LMWH group ($P < 0{\cdot}01$)*. LMWH was thus statistically significantly better than dextran 70 in preventing DVT in the legs. It was not firmly established whether this benefit was also valid in the high ileofemoral region. Two patients with non-fatal pulmonary embolism were found in each group. Per- and postoperative blood loss and blood transfusion requirements were significantly lower in the LMWH group.*

Keywords: Postoperative deep vein thrombosis, total hip replacement, heparin fragment, low molecular weight heparin, dextran 70

Deep vein thrombosis (DVT) develops in 50–60 per cent of patients undergoing elective hip replacement without prophylaxis, and fatal pulmonary embolism occurs in 1–5 per cent[1]. Prophylactic treatment seems desirable in these patients, but consensus has been difficult to reach for several reasons. Many orthopaedic surgeons are reluctant to use prophylaxis with either standard heparin or dextran, for fear of bleeding and concomitant infectious complications[2–4]. Both low-dose heparin and dextran 70 can reduce the risk of fatal pulmonary embolism in elective hip surgery, and the two methods seem to be equally effective in this respect[5]. Low molecular weight heparin (LMWH) has been in focus for some time, owing to its favourably high anti-factor Xa·anti-factor IIa activity ratio, which hypothetically implies an improved antithrombotic potential with fewer bleeding side-effects[6]. This has been shown in animal experiments but clinical results are not clearcut[7,8].

The aim of this study was to compare the efficacy of a LMWH and a dextran 70 regimen in preventing DVT in the legs, in patients undergoing total hip replacement.

Patients and methods

The study was designed as an open, randomized, controlled, prospective trial, comparing a LMWH and a dextran 70 regimen. Consecutive patients over the age of 40 years admitted for total hip replacement were studied. Exclusion criteria were: bleeding disorder, a history of septic endocarditis; allergy to iodine, heparin or dextran; manifest cardiac, renal or hepatic insufficiency; intake of acetylsalicylic acid 2 weeks before operation or anticipated need of anti-inflammatory drugs during hospitalization Patients with consecutive operations on both hips were included once only. The patients were randomized using sealed envelopes. DVT associated risk factors were recorded. Informed consent was obtained from all patients.

Prophylactic methods

The drug under investigation, LMWH fragment (Kabi 2165, Fragmin® KabiVitrum AB, Stockholm, Sweden) was prepared by partial nitrous acid depolymerization of pig mucosal heparin. The average molecular weight was 4000–6000. Anti-factor Xa activity was 160 units/mg and APTT activity was 40 units/mg, a ratio of 4. The LMWH was prepared in prefilled syringes of 0·2 ml, with a potency of 12 500 anti-factor Xa units/ml. The LMWH group received 2500 anti-factor Xa units Fragmin subcutaneously twice daily for 7 days The first injection was given 2 h before operation

The reference drug was dextran 70 (Macrodex®, 6 per cent in 0·9 per cent NaCl, Pharmacia AB, Uppsala, Sweden), of which 500 ml was given during operation, another 500 ml within 6 h postoperatively, and 500 ml on the first and the third postoperative days. Before the first dextran 70 infusion, 20 ml of a monovalent haptendextran, Promiten® (15 per cent dextran 1, molecular weight 1000, Pharmacia AB, Sweden), was injected intravenously to prevent allergic reactions from dextran 70.

All patients were mobilized on the first postoperative day, and physiotherapy was given daily

Blood sampling and laboratory analyses

Anti-factor Xa activity was analysed in an initial group of 14 patients receiving LMWH Blood samples were taken for analysis pre-operatively, during operation, 1 h postoperatively, each morning before injection and 4 h after the morning injection during the treatment period. The citrated samples were immediately centrifuged to obtain platelet-poor plasma and stored at −70°C Anti-factor Xa activity was analysed using an amidolytic method and the chromogenic substrate S-2222 (KabiVitrum AB, Stockholm, Sweden)[9].

Hip surgery techniques

Charnley, Exeter and PCA prostheses were inserted using an anterolateral incision, except for a few cases where the lateral approach, with osteotomy of the greater trochanter, was used. All patients had two vacuum drains inserted. These were removed on the second postoperative day, unless excessive bleeding (>200 ml) had occurred during the previous 24 h.

Assessment

DVT was detected by ^{125}I-fibrinogen leg scanning[10]. After oral potassium iodide, each patient received 110 μCi ^{125}I-fibrinogen intravenously on the day before surgery; when needed this dose was repeated within the first week. Radioactive fibrinogen uptake test (RFUT) was

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Table 1 *Characteristics of patients in the two treatment groups*

Characteristic	LMWH ($n = 49$)	Dextran 70 ($n = 49$)
Age (years)	66·4 ± 6·9	67·9 ± 7·0
Weight (kg)	75·2 ± 11·2	72·8 ± 11·6
Sex (male/female)	26/23	21/28
Varicose veins	4 (8)	2 (4)
Previous fracture/operation	9 (18)	11 (22)
Previous DVT/PE	2 (4)	5 (10)

Figures for age and weight are mean ± s.d.; percentages are given in parentheses, DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin

done on a daily basis for 2 weeks. RFUT was considered positive if counts at any site differed by 20 per cent or more from those at the adjacent points on the same leg and if this difference persisted or increased within 24 h. The first 10 cm close to the groin were not scanned because of interference from isotope-labelled material in the urinary bladder and operative haematoma in the hip region. Positive RFUT was followed by ascending phlebography[11]. The finding of constant filling defects, well defined and sharply outlined, was taken as the criterion for fresh DVT[12,13]. All phlebograms were re-evaluated by one experienced radiologist, with no knowledge of the particular prophylactic regimen

Ventilation/perfusion scans were not done routinely, but only if pulmonary embolism was suspected clinically All patients were physically examined 6 weeks after operation in a search for late thromboembolic events

Blood loss and complications

The intra-operative blood loss was estimated by the anaesthetist as described previously[8]. Postoperative blood loss in drains was measured daily for the first two postoperative days Haematoma in surgical wounds or at injection sites, as well as other complications related to surgical or generalized bleeding, were registered by nurses Haemoglobin level and platelet count before operation and 1 week postoperatively were recorded, together with the total volume of blood transfused. Wound rupture, infection or allergic complications were also noted.

Statistical analysis

Comparison between treatment groups was done with the two-tail Student's t test and two-tail Wilcoxon rank sum test. For comparison of qualitative variables, statistical evaluation was performed by means of the χ^2 test and Fisher's exact test The material was analysed with respect to thrombosis through cross-tabulation of prophylaxis *versus* possible risk factors Data are presented as mean ± s.d., $P < 0{\cdot}05$ was considered statistically significant

Results

Patient population

Of the 113 patients who were asked to participate in the study, 12 failed to meet the entry criteria, so that 101 patients were admitted to the trial. Three patients were excluded after admission, one because of changed operation date and two after treatment was started—one in the dextran group because of the patient's refusal to undergo phlebography, and one in the LMWH group because of surgical problems. The data of 98 patients, equally distributed in both groups, were analysed on an 'intention to treat' basis. No patient was excluded because of errors in the administration of prophylaxis Before and during surgery all patients received the correct regimen, but three of the LMWH patients missed one postoperative injection. All dextran patients had correct prophylaxis.

The two groups did not differ significantly in terms of age, weight, previous fracture or operation of the lower limb (*Table 1*). There was a slight male predominance in the LMWH group (*Table 1*). A previous history of DVT (*Table 1*) was more frequent in dextran-treated patients, and varicose veins were more frequent in the LMWH group. This bias of risk factors was considered in the final analysis. Other possible risk factors such as paresis, previous cerebral haemorrhage and cardiac infarction were rare, but evenly distributed. No malignancies were registered. The two prophylaxis groups were comparable in terms of diagnosis, type of prosthesis and anaesthesia (*Table 2*). The mean duration of operation and hospital stay were similar in the two groups (*Table 2*).

Incidence of DVT

DVT was detected in 10 of 49 patients (20 per cent) in the LMWH group, and 22 of 49 patients (45 per cent) in the dextran group ($P < 0{\cdot}01$ by Fisher's exact test) (*Figure 1*) The data were also analysed for risk factors likely to predispose for DVT. Previous DVT was more frequent in the dextran group, and statistical analysis was repeated after exclusion of these patients. The difference in DVT incidence was still significant ($P < 0{\cdot}03$ by Fisher's exact test). When both varicose vein and previous DVT patients were excluded, there was a statistically significant difference in DVT incidence at $P = 0{\cdot}02$ level (Fisher's exact test).

Table 2 *Diagnosis and details of operation in the two groups*

	LWMH ($n = 49$)	Dextran 70 ($n = 49$)
Diagnosis		
Osteoarthritis	38 (78)	37 (76)
Rheumatoid arthritis	7 (14)	5 (10)
Sequelae hip fracture	2 (4)	3 (6)
Miscellaneous	2 (4)	4 (8)
Prosthesis		
Charnley	24 (49)	25 (51)
Exeter	21 (43)	22 (45)
PCA	4 (8)	2 (4)
Anaesthesia		
Extradural	42 (86)	40 (82)
General	4 (8)	5 (10)
Combination	3 (6)	4 (8)
Duration of operation (min)	134 ± 25	131 ± 21
Duration of hospital stay (days)	18 ± 5	19 ± 5

Figures given for duration of operation and hospital stay are mean ± s.d.; percentages are given in parentheses, LMWH, low molecular weight heparin

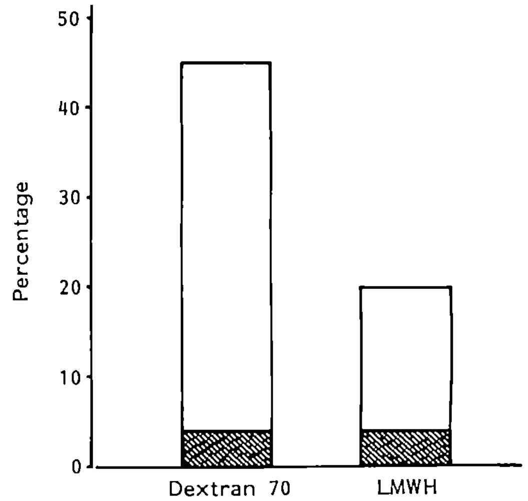

Figure 1 *Incidence of postoperative deep vein thrombosis (DVT) in 98 total hip replacement patients; 49 were given prophylaxis with low molecular weight heparin and 49 were given dextran 70 DVT was detected in 10 of 49 patients (20 per cent) in the LMWH group and 22 of 49 patients (45 per cent) in the dextran group* (P < 0·01). *Non-fatal pulmonary embolism developed in two (4 per cent) LMWH patients and two (4 per cent) dextran patients* □, *DVT*, ■, *pulmonary embolism*

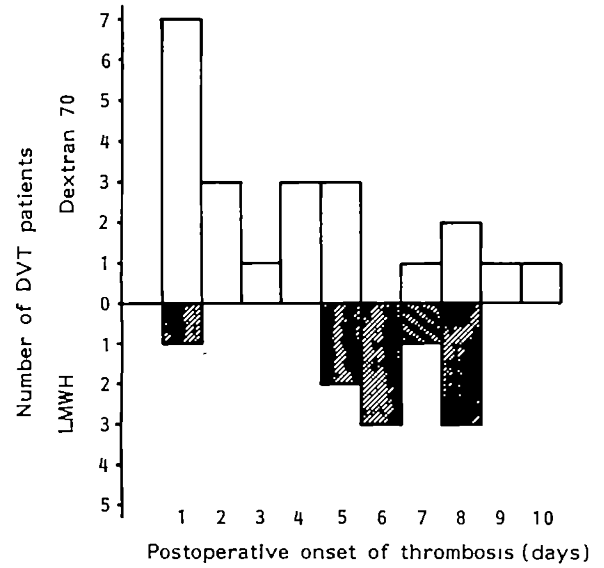

Figure 2 *Postoperative onset of deep vein thrombosis (DVT) The median period from operation to DVT onset was 3·5 days (range 1–10 days) in the dextran group and 6·2 days (range 1–8 days) in the low molecular weight heparin (LMWH) group. This difference in time interval between operation and onset of DVT was significant* (P < 0·05). □, *Dextran 70;* ■, *LMWH*

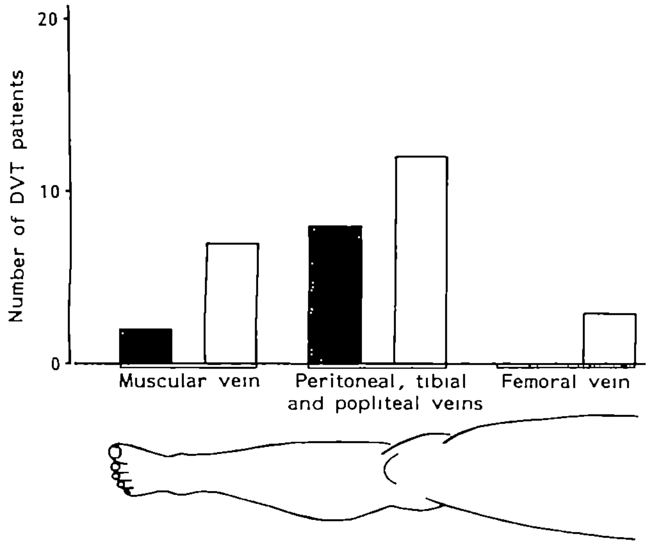

Figure 3 *Localization of postoperative deep vein thrombosis (DVT). Highest DVT level in each patient is indicated.* ■, *low molecular weight heparin patients (10 DVT patients): femoral vein DVT, 0, DVT in peroneal, tibial or popliteal veins, 8, DVT in muscular veins, 2.* □, *Dextran 70 (22 DVT patients): femoral vein DVT, 3; DVT in peroneal, tibial or popliteal veins, 12, DVT in muscular veins, 7*

Patients developing DVT were significantly older than patients without DVT; the age of DVT patients was 70 ± 6 years, and of non-DVT patients 64 ± 7 years ($P < 0{\cdot}05$). No sex difference was seen between DVT and non-DVT patients. No relationship could be found between postoperative thrombosis and obesity Cross-tabulation revealed no relationship between DVT and diagnosis, type of anaesthesia, or type of prosthesis.

RFUT was positive in 36 patients, 11 in the LMWH group and 25 in the dextran group. Positive RFUT was followed by phlebogram in all cases except one, a patient with serious bilateral pulmonary embolism and an extremely high RFUT count from the calf region in the non-operated leg. This patient was classified as having calf vein thrombosis. The DVT diagnosis was phlebographically verified in 89 per cent of the cases with positive RFUT. The median period from operation to DVT onset was 3·5 days (range 1–10 days) in the dextran group and 6·2 days (range 1–8 days) in the LMWH group (*Figure 2*). This difference in time interval between operation and onset of DVT was statistically significant ($P < 0{\cdot}05$).

In the dextran group, femoral thrombosis was found in 3 patients and below-knee thrombi in 19 patients—12 in peroneal or tibial veins, and 7 in muscular veins. In the LMWH group there was no femoral DVT, and below-knee thrombi were found in ten patients—eight in peroneal, tibial or popliteal veins, and two in muscular veins (*Figure 3*). All thrombi diagnosed in the thigh region were extensive, involving both femoral and calf deep veins. No isolated femoral DVT was found on phlebography. Eight patients, four from each group, had DVT localized in two or more deep veins in the calf region. Unilateral DVT was diagnosed in the operated leg in twenty patients and on the non-operated side in nine patients. Bilateral thrombi were found in three patients, all in the dextran group. Pulmonary embolism was diagnosed in four patients, two from each treatment group (*Figure 1*). The diagnosis was verified with perfusion and ventilation scanning. All were successfully treated with heparin infusion followed by oral dicoumarol The same treatment was given to patients with thrombosis in deep veins, except muscular veins. In all, thirteen patients in the dextran group and seven patients in the LMWH group were treated.

There was no significant difference in duration of hospital stay between the two groups, 19 ± 5 days in the dextran group, compared with 18 ± 5 days in the LMWH group. Hospital stay was significantly longer in DVT patients compared with non-DVT patients, 21 ± 5 days *versus* 17 ± 4 days. Patients treated for DVT stayed 22 ± 4 days in hospital.

All patients in this study were followed up at 6 weeks postoperatively. One of the patients with pulmonary embolism experienced symptoms 1 week after discharge and was readmitted to hospital for treatment. No other complications occurred during the period of time from discharge till follow-up.

Bleeding parameters

The mean blood loss was 1720 ± 650 ml in the LMWH group and 2210 ± 1035 ml in the dextran group, a statistically significant difference ($P < 0{\cdot}01$). The mean volume of blood transfused was significantly less in the LMWH group, 1925 ± 910 ml compared with 2480 ± 1380 ml in the dextran group ($P < 0{\cdot}02$) (*Table 3*). The mean haemoglobin 1 week postoperatively decreased by 16–17 g/l in both groups, compared with preoperative values (*Table 3*). Prophylaxis was not discontinued because of bleeding in any patient.

Haematoma in the operative region, noted as an increased thigh girth > 5 cm or bleeding through the bandage, was registered in about 50 per cent of the patients, equally distributed in both groups. Evacuation of haematoma was done in two patients in the dextran group, but there was no wound rupture or reoperation Injection site haematoma with a diameter of 5–10 mm was seen in one of the LMWH patients. Superficial wound infection, characterized by redness and secretion from the wound, was noted in two patients, one from each group. There was no deep infection or sepsis Non-surgical bleeding complications, i.e. possible systemic side-effects of the prophylaxis, were noted in four patients: erosive gastritis in

Table 3 *Bleeding parameters in the two treatment groups*

	LMWH ($n = 49$)	Dextran 70 ($n = 49$)
Total bleeding (ml)	1720 ± 650	2210 ± 1035
Transfusion (ml)	1925 ± 910	2480 ± 1380
Δ Hb* (g/l)	−17·0 ± 12·4	−16·5 ± 14·9

Values are mean ± s d., * difference in haemoglobin pre-operatively and 1 week postoperatively LMWH, low molecular weight heparin

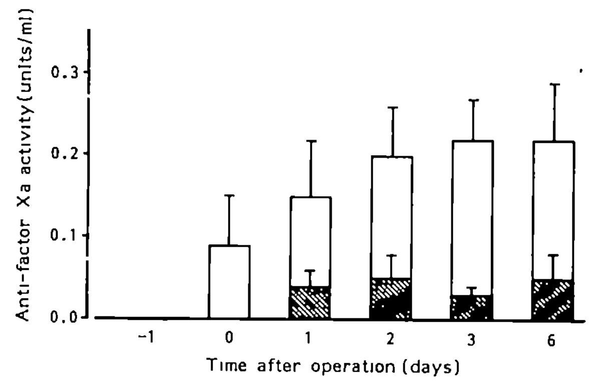

Figure 4 *Anti-factor Xa activity was measured in the first 14 low molecular weight heparin patients.* □, *Peak levels, 4 h after injection,* ■, *minimal level, 12 h after injection, values are mean ± s d.*

two patients, one from each treatment group; slight haematuria in a LMWH patient with urinary bladder catheter; and a trivial epistaxis in a dextran patient with episodes of coughing

Allergic or other complications. One patient developed an allergic erythema due to iodide tablets. No allergic reactions against dextran or LMWH were registered There was no case of thrombocytopenia.

Anti-factor Xa levels. Anti-factor Xa activity was measured in the first 14 LMWH patients (*Figure 4*). Peak levels, 4 h after morning injection, reached a plateau at 0·2 units/ml within 2 days of operation. No accumulation was found. Twelve hours after injection anti-factor Xa activity was still detectable.

Discussion

New methods are needed for prevention of thrombosis after hip surgery since the effectiveness of established prophylactic methods, such as low-dose standard heparin and dextran 70, is debated[4,14]. LMWH is very interesting in this respect.

Studies in animals and human volunteers have indicated that LMWH has an antithrombotic effect equal to standard heparin, with less influence on overall coagulation and thus reduced risk of bleeding[6,15]. Some clinical trials have not been confirmative[8,16,17], while recent studies have supported the hypothesis[7,18].

The present study compared the thromboprophylactic efficacy and safety of a LMWH and a dextran 70 regimen in 98 hip surgery patients. DVT incidence was 20 per cent in the LMWH group and 45 per cent in the dextran group. The incidence of DVT in the dextran-treated patients was in accordance with other studies[19,20]. Recent LMWH studies have demonstrated comparable incidence of DVT after hip arthroplasty[21,22]

It is difficult to compare results from one LMWH study to another Different preparations of LMWH fragments and fractions present a wide variability in molecular weight characteristics and anti-factor Xa·anti-factor IIa activity ratio. Anti-factor Xa activity represents only one aspect of heparin activity. The clinical importance of the ratio of anti-factor Xa:anti-factor IIa remains uncertain. Other properties of LMWH, such as range of molecular weight, percentage of sulphate residues, affinity to antithrombin III and effect on platelets, could also be of clinical importance, as reflected in different clinical trials[6,15,16,23–26].

Development of a LMWH standard and a standard assay method will make comparisons between different LMWH preparations more accurate in the future[25,27]. However, *in vitro* similarities between different LMWH may not be clinically relevant.

The use of dextran in the present study made a double-blind technique impossible. In spite of randomization, two risk factors for the development of DVT were unevenly distributed: previous DVT was more frequent in the dextran group, and varicose veins were more common in the LMWH group. The difference in DVT incidence postoperatively between the two prophylactic groups was still statistically significant when patients with these particular risk factors were excluded from analysis, but the *P* value was reduced from 0·01 to 0·02. Since phlebography was not performed routinely in all patients pre- and postoperatively, it could be argued that isolated ileofemoral thrombi, already existing pre-operatively, were not detected. After hip surgery the occurrence of isolated high femoral thrombi, without concomitant thrombi in the limb, seemed to be uncommon[28,29]. The statistically significant reduction in postoperative DVT in the present study after LMWH prophylaxis, as compared with dextran, was still valid after exclusion of patients with a previous history of DVT. So any pre-existing ileofemoral thrombi in the patients could not have influenced the results. The unlikely event of asymptomatic patients in either group having a pre-existing DVT in the ileofemoral region could not be ruled out. The results from the present study must thus be interpreted as follows· LMWH gave significantly less postoperative DVT in the legs than dextran It was likely that the same was true for the high ileofemoral region, but this was not firmly proven.

The median time from surgery to onset of DVT was 3·5 days in the dextran group and 6·2 days in the LMWH group. A significantly delayed onset of DVT in LMWH patients has also been reported in a comparative study of LMWH and standard heparin prophylaxis in abdominal surgery[8]. Late occurrence of DVT after total hip replacement has been reported previously[14]. This means that the diagnostic period must be extended in hip surgery patients, especially after prophylaxis with LMWH. A LMWH trial where this is neglected can be difficult to evaluate.

Is LMWH effective in preventing clinically significant pulmonary embolism without inducing bleeding complications? The present study did not answer this crucial question. It can be answered only in a multicentre trial, which would require a population of around 5000 patients[4]. The exact relationship between DVT and pulmonary embolism can be disputed, but there is strong evidence favouring the concept that effective DVT prophylaxis reduces the risk of fatal pulmonary embolization[4].

Haemorrhage was one end-point in this study. There was no difference in complications related to bleeding, but unexpectedly the blood loss and blood transfusion requirements were significantly less in the LMWH group. Dextran can prolong bleeding time and this may be of clinical importance[14,19].

The significantly higher blood loss in the dextran group could not be explained by differences in anaesthetic or operative technique (*Table 2*). Data on other relevant parameters (*Table 2*) were analysed through cross-tabulation against bleeding and transfusion, and no differences were found. There was no difference between the two prophylactic regimens in duration of surgery, a parameter that reflects the quantity of operative trauma in hip surgery. Duration of surgery correlated to total blood loss, but not to DVT.

Anti-factor Xa activity was registered as late as 12 h after injection, reflecting the long duration of LMWH. Since LMWH was given twice daily in the present study any thromboprophylactic effect beyond 12 h could not be judged Recent data from general surgical patients indicated that this could be the case[18] LMWH was given on the evening before surgery, and prophylaxis was continued with one daily injection. The antithrombotic effect was significantly better in this treatment group, when compared with conventional prophylaxis with standard heparin[18]. Since anti-factor Xa activity was measured in only 14 patients in the present study levels could not be related to the occurrence or otherwise of DVT.

In conclusion, this randomized prospective comparison of LMWH and dextran 70 in patients undergoing total hip replacement showed a statistically significantly better effect of

LMWH in preventing DVT in the legs. Whether this was valid also for high ileofemoral DVT was not firmly established. Twenty per cent of the patients in the LMWH group developed DVT compared with 45 per cent of the patients receiving dextran 70. There was no difference in complications related to bleeding between the two groups, but dextran-treated patients had greater blood loss and need for transfusion.

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Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery

In a prospective, randomized multicentre trial the efficacy and safety of the low molecular weight heparin (LMWH) fraction Fraxiparin® and unfractionated calcium heparin (Calciparin®) were compared for the prevention of postoperative deep vein thrombosis. Of 1909 patients included in the trial 1896 underwent abdominal surgery and received either one daily subcutaneous injection of 7500 anti-Xa units Fraxiparin or 5000 units calcium heparin three times a day subcutaneously. Elastic compression stockings were worn by both groups of patients in the postoperative period. Before randomization the patients were stratified in two subgroups with or without malignant disease. To assess the rate of deep vein thrombosis (DVT), ^{125}I-labelled fibrinogen leg scanning was performed daily for 7 postoperative days. Positive results were confirmed by phlebography whenever possible. Venous thrombosis occurred in 27 of 960 patients (2·8 per cent) given Fraxiparin and in 42 of 936 patients (4·5 per cent) given calcium heparin ($P = 0{\cdot}034$)*. The rates of proximal vein thrombosis were 0·4 per cent (4 patients) and 1·4 per cent (13 patients) respectively* ($P < 0{\cdot}05$)*. Pulmonary embolism occurred in 2 of 960 patients (0·2 per cent) treated with Fraxiparin and in 5 of 936 patients (0·5 per cent) treated with calcium heparin. The two treatments were equally well tolerated. Intra- and postoperative blood loss, the number of wound haematomas as well as frequency and volume of transfusions were similar in both groups. The present trial demonstrates that a single daily subcutaneous injection of Fraxiparin is more effective than the established low dose subcutaneous heparin prophylaxis with 5000 units three times per day in preventing postoperative DVT after abdominal surgery in patients wearing compression stockings.*

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Keywords: Low molecular weight heparin, Fraxiparin®, heparin, vein thrombosis, pulmonary embolism, ^{125}I-labelled fibrinogen leg scanning, thrombosis prevention, abdominal surgery

In recent years low molecular weight heparins (LMWHs) have attracted increasing scientific and clinical interest as antithrombotic drugs. Their clinical investigation has mainly been focused on the prevention of deep vein thrombosis (DVT) following surgery[1–7].

LMWHs have a different pharmacological profile from unfractionated heparin[8]. They have a longer half-life, higher bio-availability[9] and have been reported to have antithrombotic effects when administered subcutaneously once daily. However, compared with unfractionated heparin they exhibit a markedly reduced inhibition of thrombin, thus their anti-factor Xa activity is relatively more pronounced[10,11]. Further, LMWHs produce less interaction with platelets[12–14] and may induce a pro-fibrinolytic effect[15,16]. Experimentally, LMWHs produce less bleeding for an identical antithrombotic effect[17,18]. Because of these properties LMWHs were considered to be promising antithrombotic agents for the prevention of thrombo-embolic diseases[14]

The first clinical data on Fraxiparin® (Code: CY 216; Choay, Paris) came from a study published in 1982[1]. More recently the same agent was further investigated in a double-blind trial including 395 patients having general surgery and in an open study in 910 patients[3]. In the controlled trial there was a statistically significant reduction in the frequency of DVT. The frequency of DVT was reduced from 7·5 per cent in the patients given 5000 units of unfractionated heparin twice per day subcutaneously to 2·5 per cent in the patients given a single subcutaneous injection of 7500 anti-Xa units of Fraxiparin per day.

The present trial was performed to investigate the efficacy of LMWH relative to that of the low dose regimen of heparin (5000 units three times per day subcutaneously) The latter regimen represents a currently valid standard for the evaluation of the efficacy of a LMWH, since the effectiveness of unfractionated heparin has been established in a large multicenter trial[19]

Patients and methods

Patients

Men and women aged over 40 years and scheduled for elective abdominal surgery were included in the trial Other predefined inclusion criteria were: expected duration of surgery of more than 30 min and a projected hospitalization period of at least 7 days

Reasons for exclusion were: pregnancy, hypersensitivity to heparin,

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iodine or contrast medium; non-elective intervention; thyroid gland disorders, severe renal dysfunction; pre-existing coagulation disorders, thrombocytopenia, concomitant treatment with antithrombotic drugs including dextrans, active peptic ulcer; pre-existing DVT and thromboembolic events within 3 months before entering the study

The presence or absence of the following risk factors were recorded: malignant disease, cardiac disease, respiratory disease and obesity.

As elastic compression stockings were routinely used in the participating centres, they were mandatory for all patients during the postoperative period until fully mobilized. Mostly, the same type (provided by Weihermueller and Voigtmann, Bayreuth, FRG) was used.

The trial protocol was approved by the ethical committee of the University of Frankfurt and all patients gave their written consent to participate in the study

Study design

All data available in the literature during the planning phase of the study indicated a higher efficacy of Fraxiparin either by direct or historical comparison to low dose calcium heparin. Based on those data it was assumed, for calculation of the patient numbers, that 7·7 per cent of patients receiving calcium heparin will develop postoperative DVT[19] and that treatment with Fraxiparin should reduce this frequency by one-half (3·9 per cent)[1,3]. For ethical reasons the administration of radiolabelled fibrinogen was restricted to the lowest number of patients needed to confirm or reject this hypothesis. Therefore the one-sided approach was chosen and it was estimated that 900 patients per group would be required to detect a statistically significant difference at the 5 per cent level using Fisher's exact calculation (one-sided comparison, type I error rate = type II error rate = 0 05).

The trial was designed as a prospective, controlled, randomized and stratified multicentre study A total of 21 surgical departments in Germany (9), Spain (4), Belgium (2) and France (6) took part and contributed 1444, 178, 173 and 114 patients respectively The inclusion period was 27 months, from January 1985 to March 1987

The patients were assigned to treatment with either Fraxiparin or calcium heparin following a randomized schedule. Before randomization the patients were stratified in two subgroups with or without malignant disease Each subgroup and each centre was randomized individually

The trial was not performed in a double blind manner for several reasons. Dosage and rhythm of administration of the two drugs were different and two placebo injections per day in the LMWH group could not be justified on an ethical basis. In addition, thromboses were assessed by objective methods.

Treatments

The LMWH Fraxiparin (batch number 84114 DP), was obtained by ethanol extraction. It had a mean molecular weight of 4500, as determined by high performance liquid chromatography, and a specific activity of 200 anti-Xa units/mg (Institute Choay; Yin *et al*[20]). In an activated partial thromboplastin time assay the activity was 50 units/mg.

In the control group a commercial preparation of unfractionated calcium heparin (Calciparin®, Choay, Paris, batch number 84111 DP) was used The specific activity of this heparin was 170 units/mg.

Each drug was provided in prefilled syringes containing an aqueous solution of either 7500 anti-Xa units Fraxiparin in 0 3 ml or 5000 units Calciparin in 0·2 ml

The first subcutaneous injection of 7500 anti-Xa units Fraxiparin was administered 2 h before surgery. The second dose was given 8 h after surgery Subsequent injections of 7500 anti-Xa units were given every 24 h between 07 00 and 10.00 hours from the first to the seventh postoperative day.

Calciparin was administered subcutaneously 2 h before surgery in a dose of 5000 units. The second subcutaneous injection was given 8 h after surgery in the same dose. Subsequent injections of 5000 units were started on the morning of the first postoperative day and continued every 8 h up to the seventh day after surgery.

Assessments

The patients had ^{125}I-labelled fibrinogen leg scanning on the day of surgery and then daily for seven consecutive days. The thyroid gland was blocked before surgery and during the observation period using potassium iodide or Endojodin® (Bayer, Leverkusen, FRG) Each patient received 4 MBq ^{125}I-labelled fibrinogen (Amersham, UK) intravenously within 2 h after operation Scanning was performed over 11 leg positions according to the technique described by Kakkar *et al.*[21]

A positive leg scan was to be confirmed by phlebography if not contra-indicated or refused by the patient. It was predefined in the protocol that in patients with clinical signs of thrombosis but without a positive leg scan, phlebography should be performed If a leg scan was positive in positions below the knee a distal venous thrombosis was assumed. If the leg scan was positive above the knee or if it was positive above and below the knee a proximal vein thrombosis was diagnosed

The occurrence of pulmonary embolism was recorded. If pulmonary embolism was suspected, confirmation by perfusion ventilation scanning or angiography was required.

Several methods were used to assess intra- and postoperative blood loss The surgeon rated excessive intra-operative blood loss by visual impression. Postoperative blood loss was objectively assessed by recording the drainage volume as well as the number and volume of blood transfusions. In addition, the development of wound haematoma and the occurrence of macrohaematuria were documented. Haemoglobin values were recorded before and on days 3 and 7 after surgery In the event of a patient's death, the cause was investigated and confirmed by autopsy if the relatives' consent could be obtained.

Laboratory data included platelet count, thrombin time, activated partial thromboplastin time, and antithrombin III on the day before surgery and on the third and seventh postoperative days. Blood was collected 3–4 h after heparin injection. Most of the participating centres used Behring reagents (Marburg, FRG) for thrombin time, activated partial thromboplastin time and antithrombin III The assessment of blood chemistry included aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase.

Statistical analyses

The homogeneity of the two patient groups with regard to age, sex, body weight, malignant disease and type of surgery was compared by descriptive statistical methods

The frequencies of DVT in both groups were compared by means of Fisher's exact test (significance level $P = 0\ 05$; one-sided comparison) Efficacy and tolerance analyses included all patients who received at least a part of the study medication Haemoglobin levels, blood cell count and blood chemistry were assessed using repeated measures analysis of variance.

Results

Patients and operations

In all, 1909 patients qualified for the trial and were randomized. However, 13 of these patients received neither Fraxiparin nor Calciparin and therefore were excluded from analysis of efficacy and tolerance (*Table 1*).

Table 1 *Patients and operations*

Characteristic	Treatment group Fraxiparin	 Calcium heparin
No of patients		
Admitted	968	941
Not treated	8	5
Analysed	960	936
Sex		
Male	486	493
Female	474	443
Age (years)*	61 ± 12	61 ± 11
Weight (kg)*	70 ± 13	70 ± 13
Malignant disease	355 (37·0%)	349 (37 3%)
Other patients with at least one risk factor	270	252
Type of surgery†		
Gastric	104	128
Biliary	300	280
Pancreatic	20	26
Colon/rectum	214	199
Other intestine	71	87
Herniotomy	185	169
Miscellaneous	147	117
Duration of surgery (min)*	121 ± 78	123 ± 82

* Mean ± s.d., † multiple answers possible

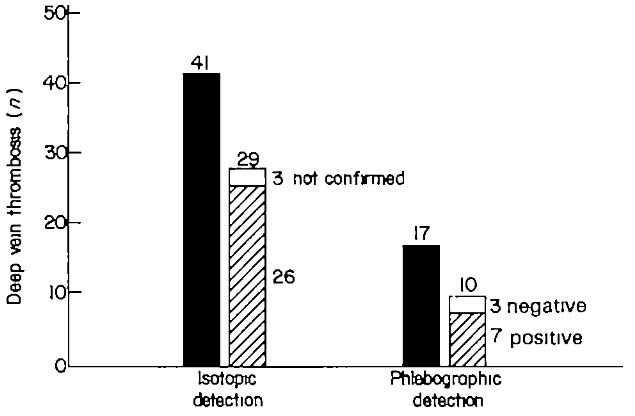

Figure 1 *Positive leg scans and number of phlebograms in the two treatment groups* ■, *Calcium heparin,* ■, *Fraxiparin*

Table 2 *Incidence of deep vein thrombosis and pulmonary embolism*

	Treatment group	
	Fraxiparin ($n = 960$)	Calcium heparin ($n = 936$)
Dose regimen per day	1 x 7500 anti-Xa units	3 x 5000 units
Deep vein thrombosis	27 (2·8%)*	42 (4·5%)*
Proximal vein thrombosis	4	13
DVT with clinical symptoms	3	9
Pulmonary embolism		
Day 0–7	1	2
After day 7	1	3
Total	2	5

* $P < 0·05$ Fisher's exact test (Fraxiparin *versus* calcium heparin)

Of the 1896 patients included, 960 received Fraxiparin and 936 were treated with calcium heparin. A total of 35 patients (21 in the Fraxiparin group and 14 in the calcium heparin group) did not receive the full study medication for various reasons; they were, however, included in the final analysis. The treatment groups did not differ in basic features such as age, sex, weight, risk factors, type and duration of surgery. Over 90 per cent of the surgical interventions were carried out under general anaesthesia The proportion of patients with malignant diseases was approximately 37 per cent in both treatment groups.

Efficacy

Isotopic DVT developed in 70 patients. Phlebography was performed in 26 of these patients (37 per cent) and in 1 patient who developed only clinical signs of DVT In the other cases patients and physicians refused this procedure owing to a lack of clinical symptoms. The percentage of patients with phlebography was equally distributed between the two treatment groups: 10 (37 per cent) in the Fraxiparin group and 17 (40 per cent) in the calcium heparin group. Three phlebograms were negative. In one of these patients the false positive leg scan was due to superficial thrombophlebitis. These three patients were considered to have no DVT. Accordingly, the number of DVTs diagnosed by these two methods was 67.

In one patient in the calcium heparin group DVT was clinically suspected although leg scanning was negative. In this case thrombosis of the iliac vein was verified by phlebography. One additional patient of the Fraxiparin group developed clinical symptoms of DVT; however, he refused leg scanning and his general condition did not allow phlebography. As the clinical signs were pronounced, he was considered to have developed DVT. Consequently the number of patients with DVT for the final analysis totalled 69. The proportion of positive leg scans and of positive phlebograms in the two treatment groups was comparable (*Figure 1*).

The difference in the frequency of DVT between the two groups was statistically significant. Of the 960 patients treated with Fraxiparin 27 (2·8 per cent) developed DVT and 42 of 936 patients (4·5 per cent) given calcium heparin developed DVT ($P < 0·05$, *Table 2*). Proximal vein thrombosis as measured in the leg scan was observed in 4 patients of the LMWH group (0·4 per cent) and in 13 patients (1·4 per cent) of the calcium heparin group. This difference was significant ($P < 0·05$). Bilateral thrombosis developed in 13 patients (Fraxiparin group: 5; calcium heparin group: 8). Clinical signs of DVT were observed in 3 patients given Fraxiparin and in 9 patients given calcium heparin. Seventy-one per cent of the DVT observed in both groups occurred during the first 3 days after surgery (*Figure 2*). The incidence of thromboses in the individual centres is shown in *Table 3*.

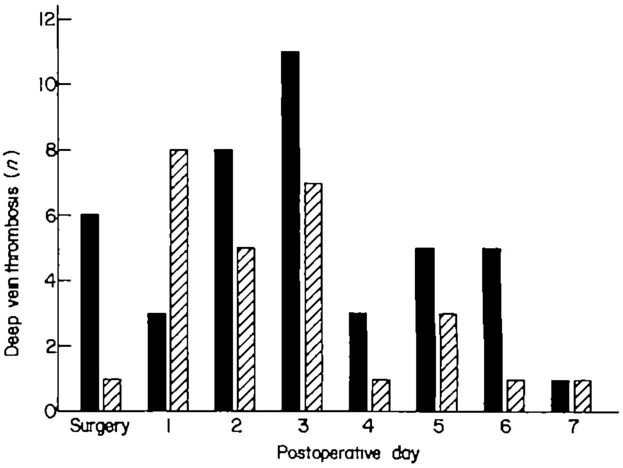

Figure 2 *Day of onset of deep vein thrombosis in the two treatment groups* ■, *Calcium heparin,* ■, *Fraxiparin*

Table 3 *Occurrence of deep vein thrombosis at the individual centres*

	Treatment with Fraxiparin ($n = 960$)		Treatment with calcium heparin ($n = 936$)	
Centre	No of patients	Patients with DVT	No of patients	Patients with DVT
1. Frankfurt	24	—	28	—
2. Bremen	110	—	108	—
3. Mainz	89	2	88	7
4. Heidelberg	22	—	27	1
5. Wuerzburg	108	5	110	5
6. Bruchsal	91	2	89	1
7. Muenchen	109	4	110	5
8. Tuebingen	80	1	80	5
9. Berlin	85	11	79	14
10. Lyon	26	—	23	—
11. Marseille I	4	—	5	—
12. Marseille II	10	—	7	—
13. Paris I	8	—	7	—
14. Paris II	3	—	3	—
15. Toulouse	6	—	6	—
16. Pamplona	27	—	23	—
17. Madrid	25	—	23	—
18. Valencia	26	—	24	—
19. Barcelona	17	2	13	3
20. Auvelais	42	—	36	—
21. Bruges	48	—	47	1
Total	960	27	936	42

Two patients treated with Fraxiparin developed clinical signs of pulmonary embolism. No further confirmation by diagnostic devices could be made in one patient who was shown clinically to have developed a pulmonary embolism 8 h after surgery. In the other patient, embolism occurred 1 day after the end of the observation period. It was verified by angiography. This patient had a positive leg scan during the study.

Five patients in the calcium heparin group developed pulmonary embolism. Clinical diagnosis was confirmed by a perfusion ventilation scan in three cases. Two of these patients had no detectable DVT. One patient developed a pulmonary embolism 2 days and the other 9 days after the end of the study. One additional patient experienced mild clinical symptoms of pulmonary embolism but was not investigated by specific methods. He developed isotopic DVT confirmed by phlebography 2 days later. One patient with bilateral and proximal DVT developed fatal pulmonary embolism on day 12 after surgery. Pulmonary embolism was confirmed as the cause of death by autopsy. The data on pulmonary embolism were not included in the primary outcome analysis.

Tolerance

The assessment of tolerance with regard to bleeding included the intra- and postoperative period (*Table 4*).

The bleeding during the postoperative period was evaluated by several means, e.g. unusual high drain blood loss or transfusion requirements as well as relaparotomy or discontinuation of treatment because of bleeding. Wound haematomas were separately reported. There was no difference between the treatment groups in terms of bleeding.

Table 4 *Tolerance with regard to bleeding*

	Treatment group	
	Fraxiparin ($n = 960$)	Calcium heparin ($n = 936$)
Patients with increased blood loss during surgery	81 (8·4%)	90 (9·6%)
Increased postoperative bleeding†	47 (4·9%)	42 (4·5%)
Patients with blood transfusion		
Intra-operative†	187 (19·5%)	183 (19·6%)
Volume (ml)*	1039 ± 658	1225 ± 927
Postoperative†	150 (15·6%)	144 (15·4%)
Volume (ml)*	964 ± 818	1033 ± 1051
Postoperative drain volume (ml)*	315 ± 437	321 ± 414
Patients with wound haematoma	83 (8·6%)	86 (9·2%)
Haemoglobin (g/100 ml)*		
Before surgery	13·8 ± 1·9	13·8 ± 1·7
3 days after surgery	12·6 ± 1·9	12·7 ± 1·8
7 days after surgery	12·8 ± 1·7	12·9 ± 1·7
Patients with macrohaematuria	96	90

* Mean values ± s.d.; † multiple answers possible

Twenty-three patients died during or within 1 month after the observation period. One patient, assigned to treatment with Fraxiparin, received no injection because he died of cardiac failure on the day before surgery. Of the other ten patients in the Fraxiparin group, six died during the observation period and four died after the study. The reasons for death were myocardial infarction (four), cardiac failure (two), septic shock (two) and advanced cancer (one). In one patient sudden death occurred on the day after surgery. Autopsy findings excluded DVT, pulmonary embolism and myocardial infarction; however, the cause of death could not be identified.

In the calcium heparin group five patients died during the study and seven died after the observation period. The reasons for death were myocardial infarction (two), cardiac failure (two), septic shock (one), advanced cancer (three), renal failure or liver insufficiency (two) and pulmonary embolism (one). One patient died suddenly on day 3 after surgery. No clinical signs of pulmonary embolism, DVT or myocardial infarction were observed. An autopsy could not be performed in this patient. Of the total of 23 patients who died during or after the trial, 13 had had malignant disease.

Laboratory results

Under treatment with Fraxiparin, activated partial thromboplastin time and thrombin time values were prolonged <5 per cent compared with pre-operative values. The average prolongation of the activated partial thromboplastin time in patients treated with calcium heparin was 10 per cent compared with the initial values. The decrease of antithrombin III levels after surgery was about 10 per cent in both treatment groups.

The levels of serum aminotransferases and γ-glutamyl transpeptidase showed a general tendency towards elevation in both treatment groups. The mean values increased by 20–30 per cent under treatment with Fraxiparin and by 25–50 per cent under calcium heparin from the day before surgery to the seventh postoperative day.

Patients with malignant diseases

Malignant disease was the cause of surgery in 694 patients. Ten patients operated on had a known malignancy which was not the cause of surgery. Patients with malignant disease underwent longer operations than patients without cancer (*Table 5*) and had a higher tendency to bleeding during and after surgery thus requiring more blood transfusions. The frequency of DVT was higher in patients with malignant disease. Furthermore, these patients were older. No pulmonary embolism was observed in these patients.

Discussion

The thrombosis incidence in this trial was 2·8 per cent in the Fraxiparin group and 4·5 per cent in the calcium heparin group. These results resemble data published by Kakkar and Murray[3]. In their study the frequencies of postoperative vein thromboses were 2·5 per cent (double-blind trial) and 2·9 per cent (open

Table 5 *Descriptive data on patients with and without malignant disease*

	Patients with cancer		Patients without cancer	
	Fraxiparin ($n = 355$)	Calcium heparin ($n = 349$)	Fraxiparin ($n = 605$)	Calcium heparin ($n = 587$)
Age (years)*	63 ± 11	64 ± 11	59 ± 12	58 ± 11
Deep vein thrombosis	15 (4·2%)	19 (5·4%)	12 (2·0%)	23 (3·9%)
Duration of surgery (min)*	167 ± 89	164 ± 87	94 ± 53	97 ± 68
Patients with excessive blood loss during surgery	57 (16·1%)	55 (15·8%)	24 (4·0%)	35 (6·0%)
Patients with postoperative blood transfusion	106 (29·9%)	107 (30·7%)	44 (7·3%)	37 (6·3%)
Postoperative drain volume (ml)*	478 ± 522	462 ± 502	182 ± 291	199 ± 267

* Mean ± s.d

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study) in the treatment groups which received Fraxiparin. In this study[3] the control group received two injections daily of unfractionated calcium heparin. In the trial presented here three injections daily of 5000 units of unfractionated heparin each were compared with one injection daily of Fraxiparin In the calcium heparin group the percentage of patients developing DVT in the present trial was lower (4·5 per cent) than expected from previously published data (7·7 per cent)[19].

With regard to the high proportion of patients suffering from malignant diseases (almost 40 per cent) who present a higher risk of developing postoperative DVT, the frequency of DVT was very low in the Fraxiparin group. Besides a significant reduction in the total number of DVTs, fewer proximal vein thromboses were observed.

The onset of DVT in this trial is in accordance with the data recorded by Gruber[22]. In both groups about 70 per cent of the thromboses occurred between the day of surgery and the third postoperative day. A previously reported delay in the onset of DVT in patients treated with a different LMWH[4] could not be confirmed

In the Fraxiparin group a lower incidence of pulmonary embolism and no fatal pulmonary embolism were observed One clinically and one angiographically confirmed pulmonary embolism occurred in the Fraxiparin group (0·2 per cent) compared with five cases (0·5 per cent) in the calcium heparin group of which three were confirmed by a perfusion ventilation scan and one by autopsy. These data indicate that Fraxiparin may prevent postoperative pulmonary embolism in patients undergoing abdominal surgery. The results obtained with calcium heparin are similar to those reported in an international multicentre trial[19] and in a Swiss–Scandinavian trial[23].

In earlier investigations different LMWHs have been compared with unfractionated heparin[1–7]. In three studies an increased tendency to bleeding in patients treated with LMWH was observed[2,4,6]. Excessive bleeding may have been caused by higher doses, as seems likely in view of the higher anti-Xa levels in the LMWH groups The agent used in the present trial did not induce an increase in haemorrhagic complications. The tolerance with regard to bleeding was very similar in both treatment groups. Also, the postoperative 10 per cent decrease in antithrombin III was comparable in the two treatment groups. An increase of serum aminotransferase levels and γ-glutamyl transpeptidase has been previously reported with low dose heparin[24]. A similar but moderate tendency could be observed in this trial. The increase was less pronounced with Fraxiparin. However, the cause and relevance of the observed changes in the transaminase levels during heparin treatment are still unclear.

The development of LMWHs as antithrombotic drugs, their biochemical and pharmacological profiles as well as their introduction to clinical use have been recently reviewed by Salzman[25] and by Hirsh *et al.*[26]. Some LMWHs apparently are as effective or even more effective than conventional heparin in the prevention of postoperative thrombosis after general surgery, as shown in this study It is still not clear why in different clinical trials of this type the percentage of patients with isotopic DVT varies between 2·5 and 17 per cent (Sasahara *et al.*[27]). Differences in patient selection or in postoperative prophylactic measures may have been responsible for some of the variations observed In this study compression stockings were applied to all patients. It is possible that the low percentage of postoperative thromboses observed was influenced by this procedure.

In this study, the percentage of thromboses varied among the participating centres. The highest incidence of DVT in both treatment groups was observed in the Berlin centre. The only major difference between patients in this and other centres is that no patients were operated on for hernia in Berlin. The method used to detect thrombi as well as the age distribution and percentage of patients with malignancies did not differ from those observed in other centres.

In most recent studies haemorrhagic complications were low in both heparin and LMWH groups. However, it still has to be established whether high anti-Xa plasma levels in single patients are correlated with an increased bleeding tendency or if other effects of heparin enhance bleeding.

The results of recent studies with different LMWHs lead to the conclusions that, for each of these agents, a different optimal dose regimen is required and that efficacy and safety as compared with unfractionated heparin are different. This may be due to the fact that these agents differ in physicochemical features such as average chain length, molecular weight distribution, sulphation degree and charge density[28]. Accordingly, a heterogeneity in the pharmacological actions of these different fractions is observed regarding protease inhibition, affinity to antithrombin III, bio-availability and half-life, interaction with platelets, antithrombic effect, haemorrhagic effect and profibrinolytic activity[29]. Therefore, each LMWH is a distinct drug and its clinical profile must be evaluated individually.

The findings of this trial show that the LMWH Fraxiparin is effective and safe in the prevention of thrombo-embolic events in patients undergoing abdominal surgery. As compared with conventional calcium heparin administered in three injections of 5000 units per day, a single daily injection of 7500 anti-Xa units of Fraxiparin reduced the incidence of DVT from 4·5 per cent to 2·8 per cent According to the statistical criteria of this investigation (one-sided Fisher's exact test), this difference is statistically significant with slightly overlapping two-sided 95 per cent confidence intervals (Fraxiparin 1·9–4·1 per cent, calcium heparin 3·3–6·0 per cent, calculated according to Pearson–Clopper[30]). Furthermore, a single injection of this LMWH per day may prevent pulmonary embolism. No higher bleeding rate was encountered after Fraxiparin treatment than was observed after treatment with calcium heparin.

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Appendix

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Intra-operative inflow resistance measurement: a predictor of steal syndromes following femorofemoral bypass grafting

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Although femorofemoral bypass grafting was originally used only as a method of limb salvage, it is now used increasingly in patients with claudication. If this trend is to be supported, the haemodynamic consequences of the operation must be carefully assessed. Fifteen patients undergoing femorofemoral grafting were studied prospectively by intra-operative measurement of the inflow resistance (IR) of the donor iliac segment. Three groups were identified by this technique. Patients with an IR<0·05 (n=*8) were uncomplicated; those with an IR ≥0·05 but <0·10* (n = *5) developed a subclinical steal syndrome; and those with an IR >0·10* (n = *2) developed a clinical steal syndrome. High initial IR values were corrected at the time of surgery in two cases. This study demonstrates that steal syndromes can occur after femorofemoral grafting and that the cause is an unmasking of previously unrecognized disease in the donor arterial segment. The measurement of IR allows the prediction of steal syndromes and their correction at the time of surgery. Direct haemodynamic studies are recommended, especially as the availability of balloon angioplasty has made inflow disease amenable to treatment.*

Keywords: Extra-anatomic bypass grafts, steal syndrome

Femorofemoral bypass grafting is now a well established method of treating unilateral iliac artery disease. Initially the operation was performed on high risk patients who were thought to be unfit for the more major aorto-iliac procedures[1]. In more recent years the indications for crossover grafting have been broadened to include lower risk patients suffering from claudication only, and some workers have gone so far as to suggest that femorofemoral grafting should be the operation of choice in all cases of unilateral iliac artery disease necessitating surgery[2,3]. Such an expansion of the role of the femorofemoral crossover graft has precipitated concern about the ability of these grafts to provide sufficient flow to the recipient limb without causing a steal from the donor limb. Although the question of steal has received considerable attention, there have been few direct haemodynamic studies of femorofemoral grafting. We have performed a prospective study of the haemodynamics of the donor arterial system of femorofemoral grafts in an attempt to isolate the cause of steal syndromes.

Patients and methods

Fifteen femorofemoral grafts performed over a 20 month period were studied. There were fourteen men and one woman with a mean age of 58·9 years (range 53–83 years). The clinical indication for surgery was claudication in nine cases and rest pain in six cases. All patients were assessed by biplanar arteriography and non-invasive Doppler studies to measure the resting ankle:brachial pressure index.

Intra-operative haemodynamic studies

The inflow resistance (IR) of the donor system was measured at operation. Blood flow in the donor common femoral artery (Q) was measured at the start of the operation using the Bristol Doppler flowmeter[4]. The brachial (P_1) and common femoral (P_2) mean arterial blood pressures were measured simultaneously using cannulae connected to a standard pressure transducer. It was assumed that the brachial arterial pressure was the same as the aortic pressure proximal to any disease in the donor iliac segment. The IR of the donor common femoral artery was calculated according to the formula:

$$\mathrm{IR} = \frac{P_1 - P_2\ (\mathrm{mmHg})}{Q\ (\mathrm{ml/min})}$$

The results were expressed in peripheral resistance units (p.r.u.) where 1 p.r.u. = 1 mmHg/1 ml per min.

Results

Arteriography

The arteriographic findings are shown in *Figure 1*. A donor iliac artery stenosis of 50 per cent was reported on the pre-operative arteriogram in four cases.

Haemodynamic results

Ankle brachial pressure indices (Figure 2). In the recipient limbs the resting ankle:brachial pressure index was increased postoperatively in all cases. In the donor limbs the index fell in 13 out of the 15 cases. In seven cases this fall was greater than 15 per cent and two of these patients developed donor limb claudication. An asymptomatic postoperative fall in ankle:brachial pressure index >15 per cent was arbitrarily defined as a subclinical steal syndrome. Thus there were five subclinical and two clinical steal syndromes in this group.

IR measurements (Figure 3). Low IR values <0·05 were recorded in the eight patients without a steal syndrome. In the five patients with a subclinical steal, IR values were ≥0·05 but <0·10 p.r.u. and the two patients who developed a clinical steal syndrome were noted to have the two highest IR values of 0·11 and 0·15 p.r.u. In two patients, intra-operative correction of inflow disease was possible. In the first case the initial IR measurement was 0·13 p.r.u. but after endarterectomy of the donor external iliac artery this fell to 0·02 p.r.u. In the second

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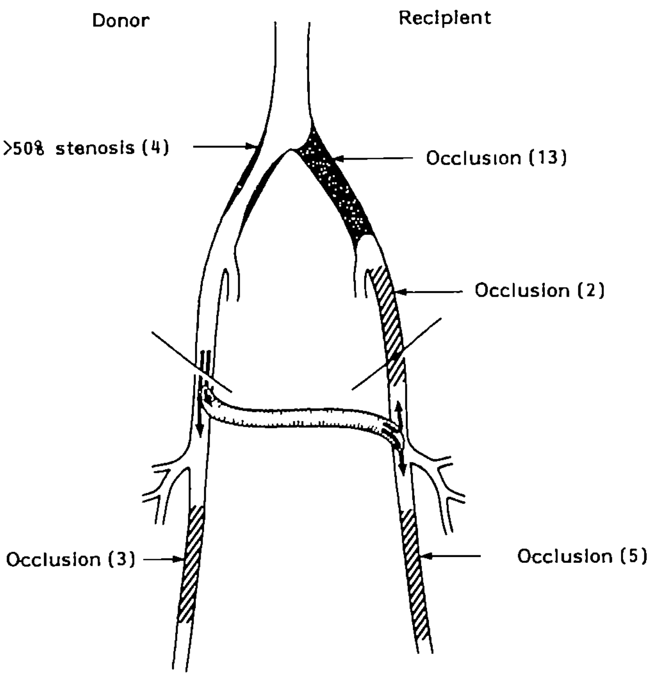

Figure 1 *The arteriographic findings are shown with the number of cases involved given in parentheses*

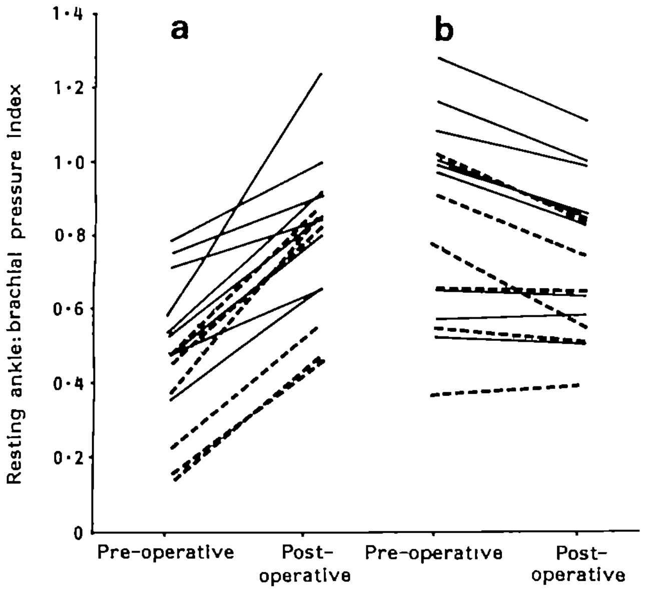

Figure 2 *Peroperative changes in ankle brachial pressure indices in* **a** *the recipient limb and* **b** *the donor limb.* ———, *Claudication,* – – –, *restpain (as clinical indication for surgery)*

case an IR of 0·10 was reduced to 0·05 by on-table balloon dilatation.

The success of arteriography in assessing the donor iliac system can also be seen in *Figure 3*. Four donor iliac stenoses >50 per cent were seen on the pre-operative angiogram. The X-ray was clearly correct in predicting haemodynamically significant disease in two cases (Nos. 4 and 15 in *Figure 3*; IR values of 0·13 and 0·15 p.r.u.). In a third case (No. 8 in *Figure 3*), the patient underwent a pre-operative Gruntzig balloon dilatation, and the final IR was 0·04 p.r.u. However, in the fourth case (No. 7 in *Figure 3*) the IR was only 0·04 p.r.u. indicating that the lesion seen on arteriography was not haemodynamically significant. In six cases Nos. 9–14 in *Figure 3*) the angiogram suggested that there was no significant inflow disease in the donor segment, but in each case a subclinical or clinical steal syndrome resulted.

Discussion

Femorofemoral grafting is of proven value in the management of ischaemia due to unilateral iliac artery disease[5]. Nevertheless, some surgeons still hold reservations about the haemodynamic consequences of these grafts. Warren and Foman[6] were the first to express concern that crossover grafting might lead to a steal phenomenon from the donor limb. Sumner and Strandness[7] were able to demonstrate a fall in donor limb ankle systolic pressure after exercise in some patients following femorofemoral grafting, but noted that such subclinical steals occurred only when the donor iliac artery was stenotic. Trimble *et al.*[8] found two patients with donor limb ischaemic symptoms following femorofemoral grafting.

The development of donor limb ischaemia postoperatively does not necessarily mean that a steal syndrome is occurring. The abolition of symptoms in one leg may unmask previously less severe arterial insufficiency in the other leg. Alternatively, damage to the donor limb femoral artery due to the application of a clamp or narrowing at the site of an anastomosis or distal embolism may result in new symptoms postoperatively. None the less, our data suggest that steal syndromes occur because of inflow disease. The primary requirement for successful femorofemoral grafting is unimpeded flow through the donor iliofemoral segment. The creation of new run-off by the graft requires an increased flow in the donor iliac artery, and in this situation lesser degrees of stenosis may become critical. It is this unmasking of previously unrecognized iliac disease that is the cause of donor limb ischaemic symptoms.

Our data demonstrate that intra-operative IR measurement can be used to predict the development of steal syndromes, with an IR >0·10 predicting a clinical steal and an IR ≥0·05 but <0·10 predicting a subclinical steal. More importantly, however, IR measurement can be used to assess the effectiveness of intra-operative attempts at treating the donor arterial disease, which is the cause of steal syndromes

Purely unilateral aorto-iliac disease is unusual, and this makes the pre-operative assessment of the donor system so crucial. The quality of the femoral pulse as judged by palpation is used by some workers[9], but flow cannot be assessed only by palpation which is unreliable in detecting mild or subcritical

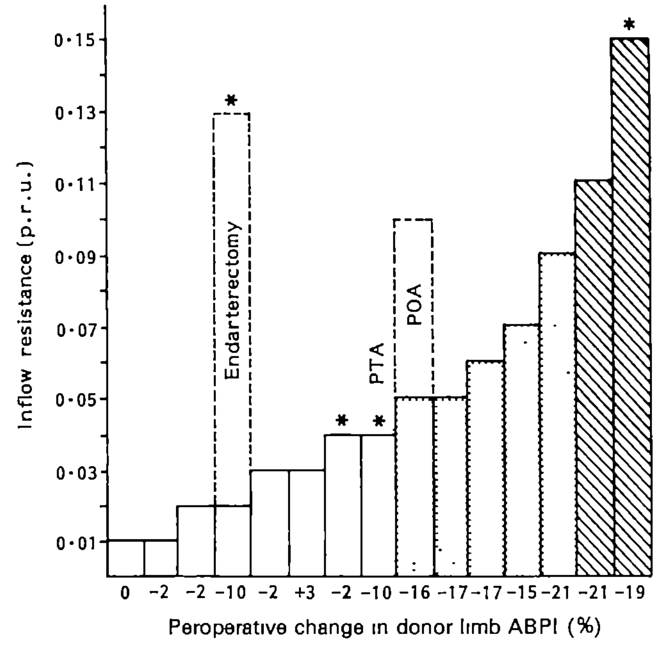

Figure 3 *The relationship between Inflow resistance (IR) and steal syndromes.* * *Greater than 50 per cent stenosis in donor iliac segment on angiogram; PTA, percutaneous transluminal angioplasty; POA, peroperative balloon angioplasty, ABPI, ankle brachial pressure index; p.r.u., peripheral resistance units* ☐, *no steal,* ⬚, *subclinical steal,* ■, *clinical steal*

iliac stenoses[10]. Uniplanar or biplanar arteriography, although useful, can also fail to demonstrate haemodynamically significant iliac disease[11]. The ideal form of assessment is direct haemodynamic study of the donor iliac artery. The intra-operative studies described here have clearly demonstrated that clinical and subclinical steals can be identified and corrected at the time of operation. The measurement of pressures alone with augmentation of flow by papaverine[12] would be a suitable alternative to our technique.

The availability of Gruntzig balloon angioplasty makes iliac inflow disease eminently treatable, and we recommend the use of direct pressure studies in the assessment of patients being considered for femorofemoral bypass grafting, especially where the indication for surgery is claudication.

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Murine monoclonal antibodies in breast cancer: an overview

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Monoclonal antibody technology has been an important development in breast cancer research. Monoclonal antibodies do not detect 'breast cancer specific' antigens but, rather, they react with normal or modified tissue antigens which are either preferentially or inappropriately expressed upon malignant cells. Thus far a number of monoclonal antibodies that have a preferential reaction with breast cancer tissue have been developed. They have a potential value in immunohistopathology as diagnostic tools and in the recognition of small quantities of malignant cells, in the development of serum assay for tumour markers in breast cancer and in the radio-immunodetection of metastases. There has been success in effecting selective targeting of anticancer agents (cytotoxic drugs, toxins, radionuclides) to tumour deposits and encouraging results are obtained in preclinical in vivo *studies. Various clinical studies are now in progress to evaluate the role of monoclonal antibodies in the management of breast cancer.*

Keywords: Monoclonal antibodies, breast carcinoma

Carcinoma of the breast remains the leading cause of mortality among western women and its incidence is increasing[1]. The production of monoclonal antibodies by Kohler and Milstein[2] has stimulated much interest in both biology and medicine and such antibodies are beginning to have important implications in current surgical practice. Monoclonal antibodies to breast cancer antigens could be useful in early detection and better prognostic subclassification and in monitoring of disease activity as well as therapy. Since there has been no dramatic change in the 10-year survival rate over the past 40 years despite many innovations in therapy[3], and as the cause of breast cancer is not known, strategies that address early detection of the disease or recurrence enabling prompt treatment are important. In addition, as patients with metastatic breast cancer are frequently treated with a variety of hormonal and chemotherapeutic agents, it is desirable to have an objective method of assessing response to treatment. Development of a serum test based on monoclonal antibody may be a step towards these objectives. Furthermore, some patients with early breast cancer have a high risk of developing distant metastases and may benefit from adjuvant therapy. Currently, the best indicator of this is the involvement of axillary lymph nodes, the detection of which requires axillary dissection with its accompanying morbidity. An alternative approach to identify nodal metastases may be immunoscintigraphy using a radiolabelled antibreast cancer antibody to identify tumour antigen on the surface of breast cancer cells. Furthermore, the relative specificity of monoclonal antibodies may be used to selectively target anticancer agents (cytotoxic drugs, toxins, radionuclides) to metastatic deposits. This review will evaluate progress in these directions and the problems encountered.

The technique of producing monoclonal antibodies has changed little since the original report[2] and is based on the principle of fusing stimulated B cells (from the spleen of a mouse or rat immunized with the appropriate antigen) with drug-selected non-immunoglobulin-secreting murine myeloma cells The resultant hybrid cells can be cloned, propagated and selected on the basis of immunoglobulin secretion, isotype and immunoreactivity. The antibodies in the monoclonal antiserum are of uniform specificity and are biochemically homogeneous. Monoclonal antibodies are thus monospecific and can discriminate between variations in a complex antigen. The main aim of the hybridoma technology is to produce immortalized continuously growing cell lines generating high affinity antibody of a required specificity and in limitless quantities.

To date, many monoclonal antibodies reactive with breast cancer have been described, but most of them also react with normal breast tissue, other normal tissues and other tumours, although generally to a much lesser degree than with breast cancer[4]. Thus monoclonal antibodies do not detect 'tumour specific' antigens; rather, they react with normal or modified tissue antigens which are either preferentially or inappropriately expressed on malignant cells. In addition, heterogeneity exists in the expression of tumour antigen in the cells of a tumour and its metastases, and between different tumour masses of different patients. There is, therefore, the potential for variable reactions of antibodies with both primary tumour and its metastases. It is clear that the ideal monoclonal antibody, reacting with all cells of all breast cancers and not with other cells, has not been achieved although 'cocktails' of monoclonal antibodies may almost achieve this. None the less, monoclonal antibodies do appear to offer a number of clinical advantages.

Development of monoclonal antibodies to breast cancer

Immunogens used to produce breast cancer-associated monoclonal antibodies

A wide range of antigens associated with breast cancer have been identified. These antigens can be conveniently divided into two categories based on the immunogen used to produce the monoclonal antibodies (*Table 1*).

A. Membrane molecules of transformed or neoplastic cells. Most of these are glycoprotein or glycolipid in nature. These antigens have been recognized by antisera against: (a) *in vitro* grown breast cell lines, (b) metastatic or primary breast cancer cells, or (c) breast cancer cell membrane extracts (*Table 1*). Monoclonal antibodies in this group include 3E1·2 which reacts strongly with membrane and cytoplasm of breast cancer and

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Table 1 *Monoclonal antibodies reactive with breast carcinoma*

Immunogen	Monoclonal antibody	Antigenic determinant	Reference
Membrane molecules of transformed or neoplastic cells	MBr 1, 2, 3	Unknown	5, 6
	24-17·1	MW $9{\cdot}5 \times 10^4$	7
	24-17·2	MW 1×10^5	7
	3E1·2	High MW glycoprotein ($>3 \times 10^5$)	8, 9
	DF3	High MW glycoprotein ($>3 \times 10^5$)	10
	NCRC-11	High MW glycoprotein ($>4 \times 10^5$)	11, 12
	B series of monoclonal antibodies including B6·2, B72·3	B6·2 on MW $6{\cdot}2 \times 10^3$–9×10^4 protein, B72·3 on MW $2{\cdot}2 \times 10^5$–4×10^5	4
	MA series	High MW glycoprotein ($>2 \times 10^5$)	13
	F36/22	High MW glycoprotein ($>3 \times 10^5$)	14, 15
Milk fat globule membranes	HMFG1, HMFG2	High MW glycoprotein ($>4 \times 10^5$)	16, 17
	M3, M8, M18, M24	Unknown, but M8 reacts with high MW glycoprotein ($>4 \times 10^5$)	12, 18
	MAM series including 115D8	Some recognize a high MW component	19
	Mc3	MW $4{\cdot}6 \times 10^4$ glycoprotein	20
	Mc5	MW 4×10^5 glycoprotein	20

with luminal membrane of normal breast[8]. The 3E1·2 monoclonal antibody is particularly useful because it reacts strongly with more than 90 per cent of breast cancers by immunoperoxidase staining on formalin-fixed sections whereas normal breast ductal epithelium only reacts weakly. 3E1·2 also reacts with both formalin-fixed and fresh breast tissue, unlike many antitumour monoclonal antibodies which only react with unfixed tissues. Thus, screening tissue sections with 3E1·2 is simple and can be applied to stored tissues[8]. DF3 and NCRC-11 monoclonal antibodies were produced against human breast cancer metastases and immunoperoxidase staining has demonstrated the presence of DF3 antigen on the apical borders of secretory mammary epithelial cells and in the cytosol of less differentiated malignant cells[10]. The antigen recognized by NCRC-11 has a specific distribution in normal tissues similar to that of antibodies raised against human milk fat globule (HMFG) membrane and is expressed on the luminal surface of exocrine gland epithelium[11]. The monoclonal antibody 24-17·2 detects an antigen which appears to be specific for breast tissue and reacted preferentially with breast carcinomas but not with other carcinomas tested[7] The recently described MA series of monoclonal antibodies also reacted with a high proportion (80 per cent) of the 25 fresh primary breast cancers tested[13].

B. Milk fat globule (MFG) membranes. HMFG membrane is derived from the apical membrane of breast epithelial cells during the process of milk secretion and envelops the fat of milk. Monoclonal antibodies (HMFG1, HMFG2) against MFG have been developed after immunization with delipidated MFG[16,17]. Other monoclonal antibodies raised against antigens in this group include M3, M8, M18, M24, MAM series and Mc3 which are raised against HMFG membrane[18–20] The antigens detected by these monoclonal antibodies are considered to be cell surface differentiation antigens in breast epithelial plasma membrane, be these cells normal, neoplastic, fibro-adenomatous or dysplastic[21].

Breast cancer-associated monoclonal antibodies

The monoclonal antibodies listed in *Table 1* are all directed to membrane antigens Although none of the antigens recognized by monoclonal antibodies appears to be absolutely tumour-specific, there are several apparently immunodominant antigens on breast cancer cells defined by such antibodies. Antigens that are secreted or shed by breast tumour cells may be useful in preparing serum tests for breast cancer while antigens that are on the cell surface of breast cancers and are not shed may be excellent targets for immunoscintigraphy. Antigens that internalize rapidly from the cell surface into endocytic vesicles would appear to be the best targets for monoclonal antibody immunotargeting of cytotoxic drugs, toxins or radionuclides.

Monoclonal antibodies not specific for breast cancer but reacting with intracellular components (such as the intermediate filament proteins) and with extracellular matrix component found in the vicinity of the tumour are also described and are being used in tumour diagnosis and localization The cytokeratins which form the intermediate filaments of epithelial cells are members of a large family of proteins. Since these proteins are only found in epithelial (and mesothelial) cells, they can be used to discriminate between carcinomas from different tissues and to identify the target cells within a tissue[22,23].

Monoclonal antibodies to high molecular weight glycoproteins

Many of the monoclonal antibodies listed in *Table 1* react with carbohydrate antigens[24], a feature of interest as alterations in carbohydrate residues have been observed in differentiation[25] and in malignancy[26]. Thus the immunodominant antigen in HMFGs, breast cancer membrane extracts and breast cancer cell lines is a high molecular weight glycoprotein ($>2 \times 10^5$–4×10^5). This large glycoprotein antigen is a mucin-like molecule, containing at least 50 per cent carbohydrate[27] and the antigenic determinants were thought to be primarily on the carbohydrate side-chains. However, very recently HMFG2 monoclonal antibody has been found to react with the stripped core protein as well as with the carbohydrate side-chains. Thus far, many monoclonal antibodies showing potential as clinically useful reagents are directed against epitopes on this high molecular weight mucin-like molecule[4,9–20,28–35]. This molecule is a major glycoprotein of HMFG membrane but is also expressed, often in an altered form, on breast carcinoma cells. The monoclonal antibodies against breast cancer that react with carbohydrate residues may be reflecting changes in protein glycosylation associated with the malignant change[24].

More recently, a mucin molecule ($>4 \times 10^5$) which carries tumour-associated epitopes recognized by monoclonal antibodies HMFG1 and HMFG2 has been purified from human skimmed milk and then treated with hydrogen fluoride to remove all O-linked sugars to reveal a dominant polypeptide (about $6{\cdot}8 \times 10^4$) which appears to be the size of the mucin core protein with attached N-linked carbohydrate. Monoclonal antibodies have been developed that react with the stripped and partially stripped core protein. From the initial screening on histological sections, one of these antibodies, SM-3, reacts with 91 per cent of breast cancers but shows little or no reactivity on benign mammary tumours or normal breast tissue. It appears that this antibody is reacting with an epitope that may usually be masked by oligosaccharide moieties in normal cells but which is exposed, perhaps because of aberrant glycosylation, in malignant cells[36]

Antireceptor antibodies

Recent investigations have demonstrated the utility of monoclonal antibodies directed against specific receptors.

A. Monoclonal antibodies to oestrogen receptor (ER). Anti-ER monoclonal antibodies have long been sought in an attempt to simplify ER analysis of individual breast tumours, and antibodies[37–39] that recognize different antigenic determinants on the ER have been used with immunohistochemical techniques to visualize the presence or absence of ER. The development of monoclonal antibodies against the ER permits direct antigenic recognition of the receptor protein independent of steroid-binding activity which may reflect the percentage of tumour cells present in the sample rather than the amount of ER per tumour cell. Such assays based on direct antigenic recognition also permit the detection of ER in the presence of oestrogens or anti-oestrogens and eliminate the potential interference in ER detection caused by other steroid-binding proteins. However, measurement of receptor content using antibody staining is only semiquantitative, being dependent on both the intensity of nuclear staining and the percentage of tumour cells stained. Studies to correlate quantitative data from biochemical assays with immunohistochemical assays are important and there are a few recent reports which demonstrate that monoclonal antibody staining of cytological smears compares favourably with the standard biochemical assays in assessing the ER content of primary breast cancer, provided the smears have adequate cellularity and are well preserved[40,41]. This, if proved, may be most useful because, by sampling several different segments of the tumour with fine needle aspiration cytology, it may provide a more detailed account of the tumour receptor content, eliminating problems relating to tumour heterogeneity. The receptor status is important because patients with metastatic breast cancer are more likely to respond to hormonal therapies if their tumours are ER rich[42]. A commercially available enzyme immunoassay (Abbott ER-EIA Monoclonal) has been developed and a good correlation was found between the ER-EIA and currently existing steroid-binding methods[43,44]; however, the ER-EIA appeared to measure more ER quantitatively. It is possible that under clinical conditions the ER-EIA is able to determine filled and unfilled sites whereas the steroid-binding assay may partially underestimate receptors because some are filled (or become filled when steroid dissociates from plasma protein during homogenization). An alternative is that the ER is partially degraded during tumour collection and storage. This could result in reduced ligand binding to the receptor, i.e. an underestimation of receptor by conventional techniques; but the monoclonal antibodies can still recognize their epitope. The ER-EIA result could therefore reflect the total content of intact and partially degraded receptor. On the other hand, the ER-EIA may also be detecting biochemically processed receptor that is no longer capable of binding steroids and is part of the normal subcellular destruction process. Only future research will resolve these various alternative hypotheses.

B. Monoclonal antibodies to transferrin receptor. A ubiquitous antigen also present on breast cancer cell lines is the transferrin receptor; normal as well as malignant tissues undergoing proliferation express transferrin receptors[45–47]. In contrast to the mucin differentiation antigen, which is restricted to epithelial cells, the transferrin receptor is a functional molecule present wherever increased proliferation or a special need for iron is present. Monoclonal antibodies reactive with breast cancer cell lines and with the transferrin receptor have been produced and studied[28].

C. Monoclonal antibodies to epidermal growth factor (EGF) receptor. An antigen present on a fraction of poorly differentiated breast tumours is the receptor for EGF. The EGF receptor is a glycoprotein of molecular weight $1{\cdot}75 \times 10^5$ (Reference 48) and is found on the cell surface and within intracellular vesicles. Monoclonal antibodies have been developed against EGF receptor and are used in immunoperoxidase assays to detect the presence of EGF receptors. While more differentiated breast cancer cell lines such as MCF7 and ZR75-1 have either few or no EGF receptors[49,50], about 35 per cent of primary breast carcinomas show high levels of the antigen, and tumours which lack ERs, are metastatic to axillary nodes or exhibit high histological grade tend to express EGF receptors. Similarly, metastatic breast cancer lesions are more frequently positive for EGF receptors than primary tumours[51,52]. In addition to breast cancer, the antigen is found in a variety of other neoplasms, including squamous lung cancers and invasive bladder tumours, and some normal epithelial tissues[53–55].

Monoclonal antibodies to carcinoembryonic antigen (CEA). One class of antigens, the so-called oncofetal antigens, are tumour cell products which are associated with fetal and malignant tissues. This includes CEA, which is a glycoprotein of molecular weight $1{\cdot}8 \times 10^5$ found originally in tumours of the gastrointestinal tract but subsequently discovered in a large number of different tumours (including the surface membrane of breast cancer cells) and in some fetal and normal adult tissues[56,57]. Murine monoclonal antibodies have been prepared to at least six distinct epitopes on CEA[57–69], which also appears to have a unique primary sequence.

Monoclonal antibodies to other breast-associated antigens

The milk proteins, casein, α-lactalbumin and lactoferrin, are unique products of fully differentiated mammary epithelium but do not appear to be synthesized or secreted by breast cancer cells Monoclonal antibodies recently made against casein may permit retesting for this marker in breast cancer frozen sections and sera[70], although a recent study with these murine monoclonal antibodies to human β-casein failed to show any expression of this milk protein in human breast cancer[71].

Clinical applications

Immunohistopathology

Monoclonal antibodies could be useful for the detection of early or pre-invasive cancer and anaplastic cancer by analysis of their antigenic profiles through the use of immunohistochemical techniques. This is, however, dependent upon a series of highly complex variables including the specificity of the primary antibody, the particular visualization method used (peroxidase and antiperoxidase or avidin–biotin–peroxidase complex techniques), the methods of tissue fixation, and subsequent tissue processing (frozen sections *versus* paraffin embedding). Monoclonal antibodies to the breast mucins (high molecular weight glycoproteins) have been useful in the identification of the epithelial origin of tumours since most of them do not react with lymphoid tumours and normal mesothelial or endothelial cells[22,23]. Recently, a monoclonal antibody 24-17 2 prepared against the MCF7 breast cancer cell line[7] was found to react with breast cancer but not with non-breast tumours and may therefore be useful in categorizing tumours of unknown origin. Unfortunately monoclonal antibodies to breast cancer may also show cross reactivities in tissues other than breast cancer, although generally to a much lesser degree[4]. In general, the results of such immunohistochemical analyses, though often not conclusive, may provide an important starting point for the work-up and management of these patients with tumours of uncertain nature. The immunocytochemical staining of needle aspirates using monoclonal antibodies for an antigen that can distinguish normal and benign cells from malignant breast cells could be a most valuable technique but at present there are few antibodies that clearly and completely distinguish between benign and malignant cells; for example, analysis of fine needle aspiration biopsy preparations with the B72 3 monoclonal antibody has demonstrated that one of the ten benign samples was positive (although staining was confined to a metaplastic apocrine epithelium) while 17 of 21 breast cancers stained[72]. Eventually, however, a panel of monoclonal antibodies may be collected which could be useful in the detection or phenotyping of breast cancer cells in fine needle aspiration biopsy preparations.

Monoclonal antibodies, however, have a potentially useful place in the recognition of metastases in lymph nodes Using a range of monoclonal antibodies for immunohistochemical staining of lymph nodes obtained from mastectomy with axillary clearance in 50 women with breast cancer, there was a 14 per cent increase in the detection rate of metastases in lymph nodes[73] when compared with conventional haematoxylin and eosin staining. Since lymph node involvement is an important prognostic indicator in breast cancer, this increased detection rate using monoclonal antibodies could have important implications in prognosis and treatment. Indeed, a striking association was found between nodal micrometastases detected by immunohistochemistry and both recurrence and survival rate in patients with invasive ductal carcinoma of breast[73]. In another study using an antiserum to epithelial membrane antigen to examine, by immunocytochemistry, multiple bone marrow aspirates from 307 patients with primary breast cancer, micrometastases in bone marrow were found in 81 patients (26·4 per cent). Although the presence of micrometastases in bone marrow did not appear to be an independent prognostic factor, it was related to various established prognostic indices—lymph node metastases, vascular invasion and size of primary tumour— and was useful as an early predictor of bone metastases[74]. Furthermore, as the intermediate filaments of epithelial cells (the cytokeratins) are totally conserved in tumours and metastatic cells of epithelial origins, antikeratin antibodies may be ideal for detecting metastases in tissues such as bone marrow and lymph nodes where epithelial cells are not normally found[22,23]

At present, a number of different parameters (tumour size, histological type, histological and nuclear grade, lymph node metastases and ER status) are used to predict the prognosis in patients with breast cancer. None the less, 28 per cent of patients with stage I disease who had radical mastectomy eventually developed metastatic cancers[75] Several studies of different immunohistochemical staining patterns with monoclonal antibodies have attempted to correlate these parameters with prognosis, but with little success. The expression of DF3 antigen has been shown to correlate with the degree of breast tumour differentiation and ER status[76] although its prognostic value is not clear. Using HMFG1 and HMFG2 monoclonal antibodies, it has been suggested that the absence of staining in breast cancer tissue is associated with poor prognosis; however, this has not been confirmed by others[17]. Ellis *et al.* have suggested a strong relationship between the intensity of staining with NCRC-11 and patient survival—intense staining being associated with improved survival[11]; in contrast, strong staining of frozen sections of primary breast cancer with anti-EGF receptor monoclonal antibody EGFR1 may identify patients with a poor prognosis[51]. The relationships between monoclonal antibody immunoperoxidase staining patterns and the marker of differentiation, namely ER status, have been studied. It appears that the antigens recognized by monoclonal antibodies H59, MAM series, DF3, 111D5 and 3E1·2 are related to the presence of ER and are therefore probably related to differentiation, and warrant further study as prognostic indicators[11,17,76–80]. However, it should be recognized that with the present methods available for grading, although of diagnostic value, monoclonal antibodies are still unlikely to assist in determining either the degree of tumour differentiation or prognosis.

Serum assays

Monoclonal antibodies that detect tumour-associated antigens in serum could be useful for the early detection of tumour masses and for monitoring disease recurrence or response to therapy. Several monoclonal antibodies have been described which recognize circulating breast cancer-associated antigens. Of the tumour markers currently available in breast cancer, CEA is by far the most widely used in clinical practice[8,9,81–88]. Myers *et al* have found that the percentage of patients with elevated CEA levels rises progressively with the stage of the disease[85]. The major limitation of CEA has been the consistent finding that only a small minority of patients with early breast cancer (< 10 per cent) has an elevated serum CEA level, although this rises to between 50 per cent and 70 per cent when metastases are detected[85,86]. A large prospective study failed to confirm the utility of CEA for monitoring breast cancer patients[89] The most useful application of CEA immunoassays may be in the screening of cerebrospinal fluid in patients with suspected carcinomatous meningitis and positive cerebrospinal fluid assays had a high correlation with eventual carcinomatous pleocytosis[90]. Recently a new breast cancer-associated antigen, CA15·3 (a high molecular weight ($2{\cdot}9 \times 10^5$) carbohydrate), recognized by two different murine monoclonal antibodies (115D8 and DF3) has been described. While it appears to be superior to CEA in both localized and metastatic breast cancer, elevated CA15·3 levels were found in only 3·7–16 per cent of patients with stage I breast cancer, 12·5–54 per cent of patients with stage II breast cancer, 30 per cent of patients with stage III and 65–91 per cent of patients with stage IV breast cancer[81,82] In addition, there was a false positive rate within the normal population (1–5 per cent) and patients with benign breast disease (20 per cent) or other cancers (5–71 per cent).

Using a modified low pH ELISA assay, women with breast cancer were found to have elevated MAM-3 (83 per cent) or MAM-6 (88 per cent) levels compared with only 5 per cent of controls. However, six out of six women with biopsy-proven benign fibrocystic disease had elevated levels of MAM-6 defined antigens in their blood[91]. A low pH ELISA method has also been developed to measure serum levels of tumour-associated antigens detectable by monoclonal antibody HMFG1 and HMFG2. Elevated serum antigens were detected in a proportion of patients with stage I or II breast cancer (50 per cent HMFG1, 50 per cent HMFG2) and metastatic breast cancer (69 per cent HMFG1, 72 per cent HMFG2) compared with healthy controls (6·3 per cent HMFG1, 3·0 per cent HMFG2) or patients with benign breast disease (17 per cent HMFG1, 4 per cent HMFG2); however, the number of patients studied was quite small and there were only 14 patients with stage I and II breast cancer[92]. Another monoclonal antibody to breast milk, Mc3, detects a breast cancer-associated antigen shed into serum[93]. By using a sandwich radio-immunoassay with Mc3 coated on beads, the antigen was detected in ten sera of advanced breast cancer patients. However, none of these serum assays is sufficiently sensitive to detect a substantial proportion of 'early' breast cancer (stage I and II). We have developed an inhibition ELISA test based on the 3E1·2 monoclonal antibody (IgM) which detects a circulating breast cancer-associated antigen called mammary serum antigen (MSA)[8,9,83]. The serum MSA level was increased (> 300 units) in a substantial proportion of patients with breast cancer (69 per cent stage I, 78 per cent stage II, 82 per cent stage III and 89 per cent stage IV). There was a false positive rate of 2–5 per cent in the normal population, and of 18 per cent in patients with benign breast disease and a variety of other diseases, especially colorectal cancer, cirrhosis and pancreatitis[9,83]. Thus far, a large number of patients have been studied and similar results have been obtained in two separate panels of coded serum samples in a blind study[94]. A comparative study of MSA, CA15·3, and CEA has demonstrated that MSA was much more sensitive than the other markers, especially in early breast cancer[94,95]. Furthermore there was a significant fall in MSA levels with the

Table 2 *Factors affecting tumour localization of radiolabelled monoclonal antibody*

Problem/factor	Potential solution
1 Incomplete penetration of conjugate into tumours	Increase monoclonal antibody dose. ?Immune fragments. Avoid immunoglobulin M
2 Slow clearance from normal tissues of the radioactive immunoglobulin	Immune fragments are more effectively cleared from normal tissues
3 Tumour heterogeneity	Cocktails of monoclonal antibodies to multiple tumour antigens
4 Non-specific localization in liver and other normal tissues	Use monoclonal antibodies that do not cross react with liver or block non-specific uptake with cold monoclonal antibody before injecting immunoconjugate
5. Circulating antigen prevents monoclonal antibody localization by forming immune complexes	Avoid using such monoclonal antibody or increase dose of monoclonal antibody to saturate the blood antigen so that enough remaining dose can localize the tumour
6. Human antimouse antibodies restrict repetitive scintigraphy	Antibody fragments are less immunogenic than whole antibody
7. Route of antibody administration	Blood pool background often a problem with intravenous localization but not so much a problem with subcutaneous administration
8 Radioactive label	^{111}In comes closest to fulfilling the criteria for the most nearly perfect radiolabel

reduction of tumour burden by mastectomy and a 92 per cent correlation with the clinical course (progressive disease, stable disease, disease regression, no evidence of disease)[9]. In some cases the changes in MSA levels antedated disease progression by up to 7 months[83]. There is, therefore, good evidence that the MSA level correlates with the tumour burden and may be useful in detecting subclinical recurrence and assessing response to therapy. Although these figures appear promising, an important question is whether or not these recurrences could have been diagnosed using other techniques and, furthermore, whether monitoring MSA levels has provided any new information to aid in patient management above and beyond the conventional methods of follow-up. The place of MSA in screening large numbers of asymptomatic individuals as an early diagnostic test has also yet to be determined. These are issues currently being studied in our laboratory.

Radio-immunodetection of tumours

The radiolabelled monoclonal antibodies have been used for the nuclear imaging of tumour metastases, especially as the major issue in the management of breast cancer patients is the detection of regional lymph nodes and distant metastases. In this technique, breast cancer monoclonal antibodies or antibody fragments (Fab or F(ab')$_2$) are labelled with a radioisotope and injected intravenously or subcutaneously in small amounts into the body, followed by localized (axilla) or whole body scanning using radio-imaging techniques. The choice of suitable monoclonal antibodies or cocktails of antibodies, the characteristics of the available radioactive labels, the potential of the imaging instrumentations (e.g. tomoscintigraphy) and the potential complications such as the development of human antimouse antibody response are important.

Most published works are on intravenous localization which has been widely reported to locate tumours of 2 cm or above[96], but lesions of 0·5 cm have been located[97]. While the published results have been encouraging and reported instances when radio-immunodetection gave information not obtainable by the best conventional methods[98–100], it generally only detects a proportion of the known tumour deposits (detected by conventional methods of investigation). There are also the inherent problems of specificity with non-specific uptake of radiolabelled antibodies by normal tissues, and background retention of radioactivity in the blood pool if injected intravenously.

An alternative method is to use subcutaneously injected radiolabelled antitumour antibodies to delineate metastatic deposits as the axillary lymph node status is the most important prognostic factor in patients with no distant metastases from the breast cancer. A study with ^{131}I-labelled 3E1·2 (IgM) injected interdigitally in eight women with breast cancer successfully identified lymph node metastases in seven axillae with palpable lymph nodes and two axillae with impalpable lymph nodes[100]. However, further study of a larger number of patients with the same technique in Melbourne has shown that non-specific uptake by normal lymph nodes and other tissues has been a major problem.

There are numerous factors affecting tumour localization of radiolabelled monoclonal antibody injected intravenously or subcutaneously (*Table 2*). The non-specific uptake of radioiodinated 3E1·2 injected subcutaneously was initially thought to be related to the large size of 3E1 2 (IgM) or the non-specific binding to non-tumour cells via Fc receptors, but subsequent studies with IgG or with F(ab')$_2$ fragments have not brought dramatic success in lymphoscintigraphy (unpublished observations*). There are, however, several theoretical advantages of F(ab')$_2$ fragments of immunoglobulins, especially with intravenous localization, because of its faster clearance from the bloodstream and reduced non-specific interaction with human Fc receptors in normal tissues with resultant higher tumour:tissue ratios[101,102]. Experimental imaging data support this hypothesis but the data are not quantitative and the advantage in clinical studies is much less striking than in the animal studies[103]. Furthermore, there is evidence from a preclinical study that the choice of intact IgG antibody *versus* antibody fragments for kinetic reasons may be less critical by the subcutaneous than by the intravenous route[104]. There are also advantages and disadvantages of different radiolabels (*Table 3*) but indium-111 comes closest to fulfilling the criteria for the most nearly perfect radiolabel. It is cleared from the circulation faster than iodine-labelled monoclonal antibody because of its preferential uptake in liver, and this has the effect of reducing background radiation[98]. Also it appears that the linkage of indium to monoclonal antibody is relatively stable so that the proportion of administered radionuclide persisting in the tumour is higher. The result of these two factors theoretically should enhance tumour:blood ratios but has to be offset against the non-specific liver uptake which will restrict the detection of hepatic metastases. However, the superiority of indium as a radiolabel in the clinical context has yet to be proved.

Thus additional studies are required to define the sensitivity and specificity of this potentially very useful diagnostic tool. It is possible that non-specific binding sites can be saturated by injecting large amounts of irrelevant antibody non-reactive with breast cancer before giving specific antibreast cancer antibody. In a pilot study of 26 patients with breast cancer, such a strategy appears to have overcome the problem of non-specific uptake of subcutaneously administered radiolabelled antibreast cancer antibody by normal lymph glands: a sensitivity and specificity of 90 per cent respectively in detecting axillary lymph node metastases have been obtained (unpublished observations*). Other potentially useful strategies include the use of higher amounts of antibreast cancer monoclonal antibody because the penetration of the antibody from the lymphatic channels into the tumour is highly incomplete, or the use of cocktails of monoclonal antibodies to overcome the problems of the heterogeneity of tumour target cells with respect to antigenic expression. Other methods of reducing background radioactivity

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* *Unpublished observations of J. J. Tjandra*

Table 3 *Radionuclide labels for monoclonal antibody imaging*

Nuclide	Half-life	Advantages	Disadvantages
Iodine-131	8.0 days	Availability Iodine chemistry	Gamma energy *In vivo* deiodination Radiation dose
Iodine-123	13.3 h	Gamma energy Iodine chemistry	Low availability *In vivo* deiodination
Indium-111	2.8 days	Gamma energy Half-life Rapid clearance from circulation Linkage to monoclonal antibody is stable	Low availability in some places
Technetium-99m	6.0 h	Availability Gamma energy	Half-life too short Chemistry
Ruthenium-97	2.9 days	Gamma energy Half-life	Low availability

Physical data are from Lederer and Shirley[105]

include delayed imaging after the injection to improve the differential tumour concentration relative to background but this is complicated by the decline in the absolute count rate itself in the tumour with time.

Another strategy is the use of subtraction techniques which have caused considerable controversy. The advantage is that it masks the variation in vascular supply to different tissues, thereby allowing small tumours, with low uptake, to be detected. Although this improves contrast, it does so at the expense of adding artefacts and introducing further statistical fluctuations without increasing the signal. Furthermore, the isotopes used in subtraction (e.g. technetium) do not distribute in exactly the same way as normal IgG and differences between subtraction isotope and imaging isotope energies (e.g. ^{99m}Tc and ^{131}I) can lead to differences in attenuation and scattering, although this can be compensated to some extent by the use of local subtraction[96] where the factor is calculated separately for each organ of interest. This may improve contrast but it is both time consuming and open to greater bias.

Another method of interest is to accelerate the clearance of background by means of a second antibody which specifically binds to the primary imaging antibody to clear the circulation of the unbound first (radiolabelled) antibody. The immune complex thus formed is cleared from the circulation by the reticulo-endothelial system either directly or through clearance of a liposome to which the second antibody is attached before administration. Good preliminary results have been obtained in animals[106,107] but there were problems with sensitivity and specificity in clinical studies[108] and concerns that these immune complexes might damage the reticulo-endothelial system.

Hence, the techniques in radio-immunodetection require a major technological advance to greatly increase their sensitivity in detecting tumour deposits and their specificity before radio-immunodetection can be accepted as a useful clinical test. Radio-immunodetection may also demonstrate high levels of antigen concentration in the tumour which may establish the basis necessary for successful antibody-directed therapy. Ultimately, this may be the most important use of radio-immunodetection.

Therapeutic immunotargeting

There are already several reports of trials in which antitumour monoclonal antibodies (used alone) have been administered to cancer patients, often with transient or quite long-lasting clinical benefits[109,110]. However, in objective terms the effects observed cannot be described as dramatic. No monoclonal antibody treatment has yet resulted unequivocally in permanent tumour regression, and most studies reporting a clinical improvement still require independent confirmation. It is thought that in most cases the reported responses have been due to interaction of monoclonal antibodies with host-effector mechanisms which include complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. It has also been suggested that the anti-idiotype antibodies produced by patients given monoclonal antibodies may also stimulate systemic host immunity against the tumour[110]. The number of monoclonal antibodies capable of inducing all such host-mediated effects is likely to remain small, and it is by no means certain that such interactions can be amplified sufficiently to achieve a major therapeutic response. The ultimate use for monoclonal antibodies is probably for the targeting of anti-cancer agents (drugs, toxins or radionuclides of high energy emission) to tumours in a selective fashion. This aim has not yet been realized but much effort is now directed to this goal. There are several factors affecting the efficacy of therapeutic immunotargeting (*Table 4*). A high level of tumour specificity is essential; ideally all tumour cells will express the target antigen on the surface and preferably this target antigen would not be released into the circulation. Already there has been success in covalently conjugating a non-cytotoxic N-acetyl melphalan (N-AcMEL) ('prodrug') to monoclonal antibodies involved in endocytotic pathways to produce tumour-specific conjugates which are cytotoxic following internalization and lysosomal degradation within the target tumour cell. These N-AcMEL monoclonal antibody conjugates display, *in vitro* and *in vivo*, specificity and cytotoxicity[111]. Further success has been obtained in conjugating N-AcMEL to F(ab')$_2$ fragments[112]. While it appears that conjugates made with whole IgG and F(ab')$_2$ were equally effective in eradicating subcutaneous solid tumours in mice when injected intravenously, the F(ab')$_2$ fragments appear to have lower immunogenicity compared with whole IgG, which therefore suggests that the F(ab')$_2$ conjugate may have greater clinical utility. Several other cytotoxic drugs have been successfully conjugated to monoclonal antibodies and the list includes anthracyclines such as daunomycin and Adriamycin*; antimetabolites such as methotrexate, aminopterine, 5-fluorouracil and cytosine arabinoside; and other alkylating agents such as chlorambucil[113–118]. While there are obvious potential advantages in using cytotoxic drugs as the targeted antitumour agents because of the considerable experience of their use clinically and their side-effects (in unconjugated form), there are several disadvantages with regard to targeting. Some cytotoxic drugs such as Adriamycin are not very amenable to conjugation owing to the loss of their cyto-

Table 4 *Factors affecting therapeutic immunotargeting*

Tumour vascularity Tumour size Tumour antigen heterogeneity Antigen modulation Antigen turnover Circulating free antigen Monoclonal antibody binding affinity	Monoclonal antibody—isotype intact immunoglobulin *versus* fragments Coupling efficiency (of drugs, toxins or radionuclides) Pharmacokinetics Host immune response to foreign protein

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* *Adriamycin is manufactured by Farmitalia Carlo Erba Ltd., Milan, Italy*

toxic activity with conjugation. Another difficulty is posed by the relatively high intracellular concentration of the drug required to kill target cells. While this can be achieved by tissue fluid concentrations obtained in clinical use, it is necessary, in the case of monoclonal antibody targeting, for the drug to be internalized following binding of the drug monoclonal antibody conjugates to cell surface antigen sites. This demands a high antigen concentration and preferably a high antigen turnover and recycling rate at the cell surface, as well as reasonably high levels of drug substitution. To some extent the need to deliver large quantities of drug may enhance the specificity of such conjugates, since only cells bearing a high antigen density are likely to receive enough drug to result in death. Normal cells with low antigen density will bind only a small amount of conjugate and will therefore have only minimal damage.

Plant toxins (ribosome-inactivating proteins) are therefore attractive agents for targeting because they are extremely cytotoxic and, being proteins, are easily conjugated to antibodies by means of heterobifunctional reagents[119–124]. Because such 'immunotoxins' are much more cytotoxic than drug antibody conjugates, the requirement for antibody specificity is more stringent. The basic structure of most toxins, as typified by ricin toxin (from castor beans), is essentially similar, comprising two polypeptide chains (A and B) linked by a disulphide bond A prerequisite for internalization of the A chain, which inhibits protein synthesis and causes cell death, is binding of the B chain to carbohydrate-containing receptors on the cell surface. As these receptors are expressed on essentially all cells in a susceptible host, interactions between B chain and normal cells can be a major problem in using unmodified toxin monoclonal antibody conjugates[119]. 'Blocking' of intact B chain reaction with cell receptors by using excess galactose or lactose has been successful *in vitro* and in animals in preventing non-specific toxicity because the cell receptors for B chain recognize oligosaccharides[125], although the large amounts of carbohydrate needed may limit clinical use. Alternatively, ricin toxin can be coupled to monoclonal antibody in the form of a toxic A chain subunit from which the sugar-binding B chain has been enzymatically cleaved[124]. When tested *in vitro*, these ricin A chain immunotoxins are exquisitely specific for target cells which express the antigen recognized by the antibody component. However, they lack the very high cytotoxicity of immunotoxins constructed with whole toxins since the B chain also plays an important role in internalization of the A chain component[126]. The *in vitro* cytotoxicity of A chain immunotoxin can be enhanced by so-called potentiating agents (ammonium chloride, carboxylic ionophores), probably by modifying the fate of immunotoxins following their entry into the cell, although their exact mechanism of action is still unresolved[125,127,128] There has only been one report of a completed phase I clinical trial of the *in vivo* administration of immunotoxins to human subjects and in that study of patients with malignant melanoma A chain immunotoxins given alone appeared to have high potency with relatively low toxicity[121] Another approach is to supplement the A chain immunotoxin using a monoclonal antibody targeted B chain, directed either towards to the same tumour antigen as the A chain immunotoxin or to the bound A chain immunotoxin itself[129,130] The two immunotoxins can be demonstrated to have synergistic cytotoxic activity *in vitro*. There is, however, a theoretical objection in that it may be possible for free A and B chains to be released from the killed cells in a form in which they could recombine. This could conceivably result in the accumulation of intact toxin with undesirable consequences for the host when used *in vivo*.

Our approach is to use a disulphide-linked whole ricin monoclonal antibody conjugate and thereby reduce its non-specific toxicity by specific blocking of the galactose binding site of the B chain[119] and this has been shown to display *in vitro* specificity and cytotoxicity. The *in vivo* efficacy of immunotoxins produced by this particular approach has also been demonstrated by showing that they suppress and even eradicate growth of subcutaneous tumour xenografts in mice when administered intravenously or by direct intratumour injections[119]

Antibody-targeted radionuclides (radioactive isotopes with α- or β-emitting properties such as iodine-131, palladium-109, bismuth-212, yttrium-90 and astatine-211) pose technical problems of labelling and toxicity[131–136]. The theoretical advantage of delivering a lethal hit, not only to the tumour cell to which it binds but also to neighbouring tumour cells which do not bind the antibody either because of tumour heterogeneity or because of their greater distance from the sites of penetration by the antibodies into the tissues, is partly offset by its toxic effect on neighbouring normal cells. Development of this field creates a series of radiobiological problems and demands special facilities for labelling and patient isolation.

While reports of effective immunotherapy in breast cancer are lacking, there have been optimistic reports of success in other tumours such as glioma[137], malignant melanoma[121], lymphoma and leukaemia[138,139]. There are currently ongoing phase I/II clinical trials in the use of N-AcMEL monoclonal antibody conjugates used systemically for hepatic metastases and whole ricin monoclonal antibody conjugates (where the galactose binding site of the B chain has been inactivated) injected intralesionally in patients with locally advanced breast cancer in Melbourne. The results of these trials will be available shortly.

There are some other important limitations associated with monoclonal antibody conjugates (*Table 4*). These include the development of human antimouse antibody response which could restrict repetitive dosing. Other problems include occasional toxicity with fever, pruritis, bronchospasm and transient hypotension; the disappearance of tumour antigen from the surface of target cells in response to antibody binding, so-called antigenic modulation, preventing immediate retreatment with the monoclonal antibody conjugate, and development of circulating immune complexes due to the presence of large amounts of circulating tumour-associated antigen in the patient's serum. While there is a theoretical advantage to the use of human monoclonal antibodies, especially since multidose schedules will almost certainly be required, at the present time human antitumour monoclonal antibodies have poor specificity and activity and in any case a significant element of the anti-immunoglobulin response is directed towards the antibody idiotype[140]. Moreover, immune responses can be expected against carriers, against toxins and against drugs as haptens. It is not clear at present how such responses would affect therapeutic efficacy, but this information will undoubtedly come from clinical trials.

In conclusion, monoclonal antibodies developed thus far against breast cancer have led to a more systematic study of human breast cancer systems The development of sensitive and specific serological breast cancer assay, of radio-immunolocalization of metastases and of treatment modalities heralds a new and exciting era in breast cancer management Currently, the antitumour monoclonal antibodies in use are still the 'first generation' and the future development should be in the production of 'second generation' antibodies of greater specificity and affinity, and this may require the use of genetic engineering techniques. Furthermore, for the purpose of therapy, there is a need for a new generation of prodrugs of small molecular size with potent cytotoxic activity, developed especially for antibody targeting This will need the assistance of our pharmacological colleagues. However, one important issue which is often overlooked is that of cost. Monoclonal antibodies are expensive to produce and they will be required in large quantities for therapeutic trials. Fortunately there is rapid development of large scale production methods and it is to be expected that this will lead to comparatively low cost monoclonal antibodies within the next few years, so that by the time phase I and II therapy trials have been completed it will hopefully become economically feasible to produce conjugates on a large scale if the trials indicate the desirability of proceeding.

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Erratum

'Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis', by D. Bergqvist, T. Mätzsch, U S. Burmark, J. Frisell, O. Guilbaud, T. Hallböök, A. Horn, A. Lindhagen, H. Ljungnér, K.-G. Ljungström, H. Onarheim, B. Risberg, S. Törngren and P. Örtenwall, *Br J Surg* 1988; **75**: 888–891, page 888, abstract line 9: for '*5·0 per cent, P=0·02). The frequency of bleeding was 6·7 per cent among*' read '*frequency of deep vein thrombosis was significantly reduced among*'. We apologize for the technical error which caused one line to be superimposed on another. The corrected abstract is printed in full below.

Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis

A prospective randomized double-blind trial was performed comparing conventional low-dose heparin with a low molecular weight heparin fragment for thromboprophylaxis in elective general abdominal surgical patients. The first dose of the heparin fragment was given the evening before surgery, and further doses were given thereafter every evening. There were 1002 analysable patients, 826 having received correct prophylaxis. Of these 1002 patients, 64 per cent were operated on for malignant disease. A total of 20 patients died, 10 in each group. The frequency of deep vein thrombosis was significantly reduced among patients with correct prophylaxis with the heparin fragment (9·2–5·0 per cent, $P=0{\cdot}02$). The frequency of bleeding was 6·7 per cent among the heparin fragment patients and 2·7 per cent among the patients given conventional heparin ($P=0{\cdot}01$), but all bleeds were of minor degree and there was no difference in the reoperation rate for bleeding, or in the transfusion requirements. Local pain at the injection site was reported significantly less often among patients given the heparin fragment.

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Erythrocyte membrane stearic and oleic acid ratios in breast cancer

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A case control study has been conducted to determine the value of stearic/oleic acid ratios in the erythrocyte membranes of women at the time of presentation with breast cancer. No difference was found between the stearic/oleic acid ratio of cases and that of controls with benign breast condition or normal volunteers. Furthermore, within clinical stages of breast cancer, no differences were detected. This ratio does not appear to be of value as a marker of malignancy, or of tumour burden.

Keywords: Breast cancer, membrane lipids, tumour markers

Wood *et al* [1] have reported that erythrocyte (RBC) membranes from a group of patients with various types of cancer showed an alteration in the ratio of stearic (C18) to oleic (C18:1) acids compared with normal individuals. In a series of women with breast cancer this ratio was in the range 0·61–0·95, whereas in a group of control women it was 1·1–1·9. However, in subsequent studies of a variety of malignancies none of these findings could be confirmed[2,3].

Such a clear-cut test could have major implications for breast cancer screening and for monitoring of recurrence and response to treatment. For these important reasons it was deemed essential to evaluate C18/18:1 ratio in patients with different stages of breast cancer and normal controls.

Patients and methods

Patients

The investigation comprised three study groups: breast cancer cases, benign breast disease controls, and normal controls. None of the women had any medical abnormalities and in particular none was diabetic—the C18/18:1 ratio has been shown to be reduced in such patients[4].

Patients with breast cancer. This group comprised 44 women with proven breast cancer before treatment by either mastectomy or breast conservation. These patients originally had UICC stages I, II or III, and all were under the care of the breast clinic at Guy's Hospital.

Control patients with benign disease. This group consisted of 18 women with a variety of biopsied benign breast conditions. None of them had histological features known to be precursors of breast cancer.

Control normal women. All of the 30 controls were healthy female volunteers who worked at Imperial Cancer Research Fund's central laboratory.

RBC preparation

The RBC preparation membranes (ghosts) were freshly prepared using a method derived from Alexander *et al* [5] as follows: venous blood (5 ml) was drawn from all cases and controls into ethylenediaminetetra-acetic acid (EDTA) tubes. The plasma was separated by centrifugation (1200*g* for 5 min at 4°C) and then removed, after which the RBCs were suspended in 5 ml phosphate buffered saline (pH 7·2). The tubes were centrifuged three times, discarding the supernatant between each wash.

After the final saline wash, 5 ml distilled water was added to the packed RBCs, and the capped tubes were inverted several times to ensure complete haemolysis. They were then left to stand at 4°C for 1 h, followed by several more inversions, and were then centrifuged at 3000*g* for 15 min after which the supernatants were removed. The pelleted membranes were washed a further four times with distilled water, followed by a final wash with phosphate buffered saline (diluted 1 in 5). This final wash removed excess pigment from the membrane (RBC ghosts).

To the deposit in the tubes was then added 0·5 ml 2·5 M KOH in 50 per cent methanol/water. This was thoroughly mixed by Pasteur pipetting and then transferred to 10 ml glass tubes with ground glass stoppers. The air was displaced with nitrogen, the stoppers were tightly replaced, and the tubes were incubated at 65°C for 1 h. They were then cooled in ice, 1 ml water was added, followed by 0·65 ml 2 M H_2SO_4. The saponified lipids were then extracted into 3 ml heptane containing 0·1 per cent butylated hydroxytoluene. A reference standard of 0·37 mmol/l margaric acid (10 μl in heptane) was added, and the solvents were removed under nitrogen at 45°C. The extracts were then methylated with methanol containing 10 per cent boron trichloride in a stoppered tube for 15 min at 65°C. After cooling in ice, 1 ml water was added and the mixture containing the fatty acid methyl esters (FAMES) was back-extracted into 3 ml heptane which was again taken to dryness under nitrogen. To each tube was then added 40 μl *n*-nonane before gas chromatography[6].

Gas chromatography

The gas chromatograph was a Pye Unicam model 304 fitted with an on-column injector (Model OCI, SGE Ltd.) and a flame ionization detector. Analysis of the FAMES was performed using a CP Sil 88 fused silica quartz capillary column (50 m × 0·32 mm; Chrompack UK Ltd.). Injection (1 μl) was by means of a 5 μl microsyringe fitted with a silica quartz needle (No. 5A-SOC-75A, SGE Ltd.) with helium as the carrier gas (1·2 kg/cm^2). The analytical conditions were: initial temperature 160°C for 5 min, then temperature programming where a rise of 2·8°C/min takes the temperature to 220°C which is then maintained for 5 min. The complete unit was connected to a VDU computerized integrator (Pye Unicam, model SP4850), by which peak areas were measured and calculated from the reference standard (C17). Results were expressed as normalization values of the total, after calibration with standard FAMES (0·1 μg, Sigma Chemical Company Ltd., UK).

Results

A typical gas chromatographic profile of RBC FAMES is shown in *Figure 1*. The mean ages, and C18/18:1 ratios of the cases and controls are given in *Table 1*. There was no significant difference between the C18/18:1 ratios of the three groups. Although the cases and controls differed significantly in age ($t = 5{\cdot}98$, $P < 0{\cdot}001$), there was no relationship between age and C18/18:1 ratio ($r = 0{\cdot}11$).

When the breast cancer cases were subdivided into stages at presentation, again no significant difference was detected between those with stage I, stage II and stage III disease. The individual results are given in *Figure 2*.

Taken together, these results do not support the use of the C18/18:1 ratio as a tumour marker in terms of presence or absence of malignancy, or in terms of tumour burden.

Discussion

In this investigation we have not found any significant alteration in the C18/18:1 ratio in erythrocyte membranes from patients with breast cancer, those with benign breast disease, or normal women. The methodology in this study differed from that employed by Wood *et al* [1] who also carried out a benzene rather than a heptane extraction, but it is unlikely that this would account for a difference in the C18/18:1 ratio.

The results reported here were derived from freshly prepared erythrocyte membranes which had not been frozen and stored. It is not clear whether the RBC samples used by Wood *et al.*[1] were fresh or frozen. It was found in preliminary experiments that storage of RBC at −20°C resulted in inconsistent losses of certain fatty acids, in particular arachidonic acid (C20:4), so

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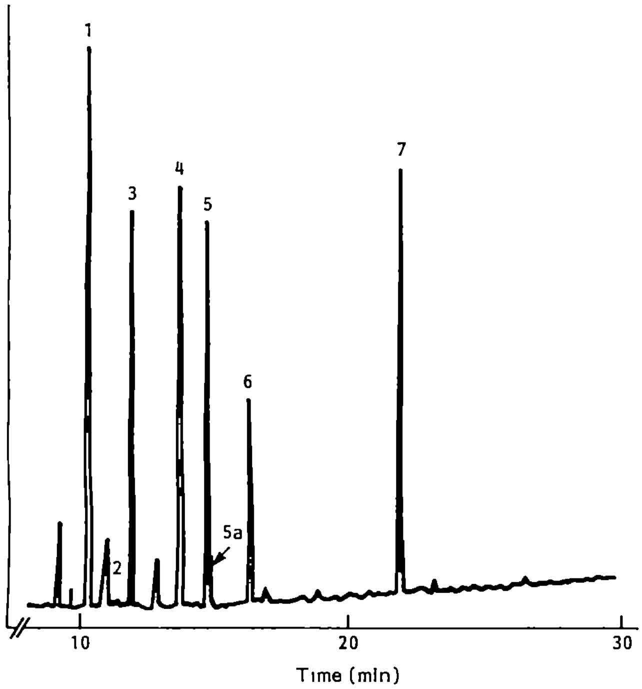

Figure 1 *Gas chromatogram of erythrocyte fatty acid methyl esters (FAMES) 1, C16 (palmitic), 2, C16 1 (palmitoleic), 3, C17 (reference standard), 4, C18 (stearic); 5, C18 1 (oleic), 5a, C18.1 (?), 6, C18 2 (linoleic), 7, C20·4 (arachidonic); all other data in text*

Table 1 *Comparison of cases and controls*

	No. of patients	Mean age	C18/18·1 ratio
Breast cancer	44	59·3 ± 1 8	1·24 ± 0·26
Benign biopsies	18	47·1 ± 3·2	1 2 ± 0·37
Normal controls	30	34·7 ± 3 3	1 1 ± 0·31

Values are ± s e m

that differences in storage time of cases and controls might yield artefactual results. Another report has already shown that storage of RBCs at 4°C for 24 h resulted in increased C18, but not C18:1, thus mimicking the diseased state[7]. Some loss of arachidonic acid also occurred.

Another difference is that we used a capillary column for the gas chromatography stage whereas Wood *et al*[1] used a conventional packed column. The latter does not give sufficient resolution to allow a separation of minor fatty acids from major fatty acid peaks, particularly in the case of oleic acid—even with the 50m CP Sil 88 capillary column separation can be achieved completely only by using a new column. Although these minor peaks may form only about 5 per cent of the total fatty acid fraction, in some specimens they can comprise considerably more The use of a more efficient column has enabled a tentative identification of some of these peaks as other C18:1 products. Although intrinsically interesting, the influence of these minor peaks probably does not account for the clear delineation between malignant and non-malignant cases as previously reported[1].

Another possible explanation for the divergence of results could be the effects of fasting on RBC membrane lipids, and therefore the timing of sampling in relation to meals could be of importance All our samples were collected between 10.00 hours and noon. A possible association of the C18/18:1 ratio with age has been suggested[2]. Our study groups were not exactly compatible for age, but we have found no evidence of any association between age and C18/18:1 ratios and neither did Neoptolemos *et al.*[8] in a recent report on colorectal cancer.

The lack of any difference between the three clinical stages of breast cancer may have been because the tumour burden between the groups was relatively low. Different results might be obtained in terminally ill cachectic patients, but such alterations would be of no value as a test for either malignancy or for monitoring a patient's progress. It is concluded that C18/18:1 ratios are of no value as a tumour marker of breast malignancy.

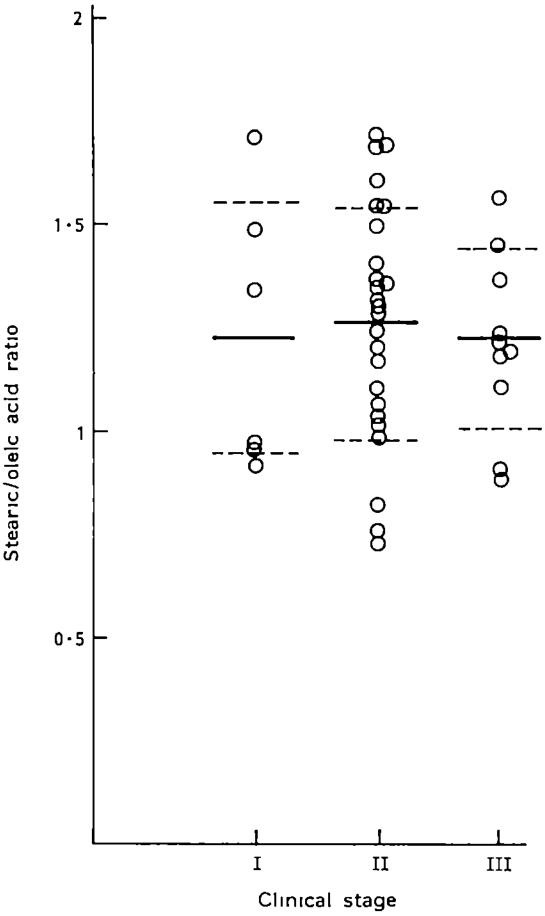

Figure 2 *Individual stearic/oleic acid ratios in patients with stage I (n=6, mean±s.d., 1 23±0·33), stage II (n=26, 1·28±0 28) and stage III (n = 11, 1·22 ± 0·20) breast cancer* ——, *Mean*, - - -, *s.d.*

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Natural history of the benign breast lump

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A prospective study of 112 patients with clinically discrete benign breast lumps has shown that 68 per cent of patients experienced resolution of their lumps over a period of up to 2 years. Resolution of both fibro-adenomas and discrete areas of fibro-adenosis was observed. Diagnosis was achieved by clinical examination and fine needle aspiration cytology. Four patients thought clinically to have benign disease were proven by cytology to have a carcinoma, but no patient with a cytopathological diagnosis of benign disease has developed cancer during or subsequent to this study. We recommend that patients under 35 years of age with clinically and cytologically benign breast lumps can be offered the option of non-excision in the reasonable expectation of resolution of their lesion.

Keywords: Cytology, benign breast disease, fibro-adenoma, fibro-adenosis, conservative treatment

The acceptance of fine needle aspiration cytology (FNAC) as an accurate diagnostic method in the management of breast disease is becoming established[1,2]. An accuracy rate of 98–99 per cent in diagnosing malignant lesions has been reported[3,4], with some series having no false positives. With such high specificity and sensitivity, the technique should be used in the diagnosis of benign lesions. Clinical application is dependent upon good technique[5] and an experienced cytopathologist[6]. Some clinics are fortunate to have a cytopathologist present to give an immediate opinion on slides. This allows repeat specimens to be obtained when preparations are unsatisfactory or if there is a discordant clinical and cytopathological diagnosis.

A definitive diagnosis of malignancy at the first clinic visit allows treatment to be planned and the diagnosis to be discussed with the patient. Since the majority of new patients attending a breast clinic with lumps have benign disease (90 per cent in our clinic), this technique allows the majority of women to be reassured.

The natural history of the discrete benign breast lump is not well studied. Teaching still dictates that all breast lumps should be excised to avoid missing malignancy[7] or to allow accurate diagnosis and reassurance of the patient. Anecdotally, fibro-adenomas are unusual after the second and third decades: are we to assume they have all been surgically removed, or do they regress in patients of 40 or more years? Diffuse areas of fibro-adenosis are known to vary considerably in size during the menstrual cycle, but even relatively well circumscribed lesions may regress with time. A few centres are beginning to address the problem of the benign lump and to question the necessity of its automatic removal[8,9]. Most have started cautiously by laying down strict criteria for observing a lump and use FNAC as the biopsy technique. Leaving a lump *in situ* allows study of the natural history of such lumps and avoids the needs for hospital admission and anaesthetic.

Whilst FNAC is not without its diagnostic pitfalls, there may be problems with the interpretation of frozen section biopsies. The combination of FNAC, clinical examination, and mammography allows the assessment of discrete benign breast lumps to be addressed prospectively. We report such a study of women seen in our breast clinic and followed for a minimum of 2 years.

Patients and methods

Women seen in the breast clinic with discrete breast lumps thought to be benign on clinical examination were entered in the study, and patients with malignant or diffuse disease were excluded. Patients with a discrete area within a background of diffuse lumpiness were also not included in the study.

Patients underwent FNAC biopsy after a history and clinical examination. The lump was clinically described as either a fibro-adenoma if it fulfilled the usual criteria (a firm, discrete lesion which was mobile in two planes) or an area of discrete fibro-adenosis if it did not.

An immediate opinion on the 'best slide' (assessed by eye—experience allows judgement of which smears are likely to contain satisfactory numbers of cells) was given after staining with Rapi-Diff II (Infrakem Ltd., UK), further slides were studied after May–Grunewald–Giemsa staining, performed in the laboratory later in the day. We have reported elsewhere the high specificity and sensitivity obtained in the immediate *versus* later reports[10]. FNAC was repeated at the first visit if the specimen obtained was unsatisfactory (i.e. no cells obtained or a discordant clinical and cytopathological diagnosis).

The six-point reporting scale was used (*Table 1*)[11,12]. AC5 lesions were unequivocally malignant, AC4 were all very suspicious, and more than 90 per cent were eventually diagnosed as malignant. AC3 lesions were usually benign but often had atypical cells—an effect often due to the contraceptive pill or to pregnancy. An AC0 smear represented no material of diagnostic value, although occasionally abundant fat cells in the absence of ductal cells confirmed the clinical diagnosis of a lipoma. AC1 represented too few ductal cells to give a definitive diagnosis, although all cells seen were benign.

The AC2 smears formed the majority of the lesions studied here. The cytopathologist subdivided the AC2 group into fibro-adenomas if a typical fibrous stroma was seen or fibro-epithelial hyperplasia if it was not. The sheets of cells seen in a fibro-adenoma were often large with finger-like branchings, and the cells were regularly distributed in a single layer with a honeycomb pattern. Other diagnostic criteria include

Table 1 *Cytopathological reporting format*

Unsatisfactory	
AC0	No ductal cells seen. Presence of striated muscle or myo-epithelial cells disregarded
AC1	Scanty ductal cells considered inadequate for diagnostic purposes
Benign	
AC2	Adequate number of ductal cells without any atypia
AC3	Benign breast disease with minor atypia
Suspicious (over 95 per cent turn out to be malignant)	
AC4	Suspicion of malignancy including cases with scanty malignant cells and well-differentiated tumours
Malignant	
AC5	Unequivocal malignancy

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Table 2 *Details of 20 patients undergoing lump excision*

	Clinical diagnosis	Histology
Patient request (11)	5 FA 6 DFA	5 FA 6 FEH
Surgeon's advice (9)	1 ?FA but AC4 2 FA but AC3 5 DFA but AC3 1 FA but mammography suspicious	Radial scar 2 FA (2 pregnant) 5 FEH (4 pill) FA

FA, fibro-adenoma, DFA, discrete fibro-adenosis; FEH, fibro-epithelial hyperplasia

Table 3 *Diagnosis on clinical grounds and subsequent cytology*

Clinical diagnosis	*n*	Cytological diagnosis	*n*
Fibro-adenoma	42	Fibro-adenoma	32
		Fibro-epithelial hyperplasia	10
Discrete fibro-adenosis	60	Fibro-epithelial hyperplasia	52
		Lymphatic tissue	3
		Lipoma	5
Total	102	Total	102

the presence of myo-epithelial cells (also known as 'bare nuclei'). Fibro-epithelial hyperplasia is an all encompassing term used by some cytologists to describe the benign aspirates which do not fall into the specific category of a fibro-adenoma. Other terms used by histologists include fibro-adenosis, fibrosis, adenosis, epitheliosis, sclerosing adenosis and papillomatosis. Histological confirmation of a cytological diagnosis of fibro-adenoma was confirmed in 81 per cent of over 250 cases studied before the introduction of this study.

Mammography was carried out in many of the patients aged 35 years and older, and in 11 patients aged under 35 and 1 under 30 years

The outpatient diagnosis was always discussed with the patient, and the choice of excision or follow-up offered. The patient was told that the standard treatment was excision but that we were examining a non-excisional policy We stressed that we would remove the lump if the patient wanted this Eleven accepted the offer of removal (*Table 2*).

Excision was advised if the cytological grade was AC3 or AC4 or if repeated FNAC was unsuccessful Patients were reviewed at variable times after the initial consultation. All were seen at least once more after 3 months, if there had been no change clinically or cytologically and the patient was educated in the technique of self-examination, they were discharged from the clinic.

Between 40 and 50 per cent of the patients were followed for up to 18 months before discharge, although the follow-up interval has subsequently lessened with experience. Patients who had undergone resolution of their lump or who were discharged with their lump unchanged were asked to attend an additional review clinic after 2 years. Age, initial and subsequent cytopathological grade, clinical diagnosis, time to resolution of the lump (if this occurred) and follow-up were recorded. At this clinic any patients with residual or new lumps underwent FNAC, and those whose lumps had resolved since their previous attendance were identified

Results

No patient with a clinical *and* cytological diagnosis of benign breast disease has re-presented with malignancy during the 4 years of study.

One hundred and twelve women were entered into this study, of whom ten were excluded from further analysis. Six failed to attend for follow-up, and four patients had a clinical diagnosis of benign disease but had malignancy diagnosed on cytology. Two of these were found to be tubular carcinomas, one lobular and one mucinous This left 102 patients with evaluable lumps The average age of this population was 33 ± 10·8 years.

Table 3 gives the breakdown of the lesion diagnosed on clinical examination and its subsequent cytology. Forty-two lumps were initially diagnosed as fibro-adenomas, of which thirty-two (76 per cent) were cytologically confirmed. The other ten were classified cytologically as fibro-epithelial hyperplasia Sixty lumps were classified as discrete fibro-adenosis, of which 52 were cytologically defined as fibro-epithelial hyperplasia, but eight lumps thought to be discrete fibro-adenosis turned out to be either lymph nodes (three lumps) or lipomas (five lumps).

Twenty patients underwent excision of their lump *Table 2* shows the reasons for this and the histology of the lesion. Eleven patients asked for excision, usually at their first visit and before any diagnosis was made. Of these five had fibro-adenoma and six had discrete fibro-adenosis. Nine patients were advised to have an excision: one because of suspicious mammography, one AC4 (histology showed a radial scar), and seven AC3 lesions (two were fibro-adenomas in pregnant women, and five women had fibro-epithelial hyperplasia, of whom four were taking the contraceptive pill). Eighty-one patients who had not defaulted or who had not undergone excision were, therefore, available for follow-up

At discharge, 26 women (23 per cent of the original study group of 112, or 32 per cent of those followed up for more than 2 years) still had a lump present and 55 (49 per cent of the original 112, or 68 per cent of the 2-year follow-up group) had experienced complete resolution of their presenting lesion. The breakdown of these groups is given in *Table 4*

The time to discharge in the first year of the study averaged 9 months but this has now fallen to 3 months. The 26 women with lumps present at discharge comprised 14 with fibro-adenoma and 12 with discrete fibro-adenosis clinically diagnosed (11 and 15 respectively, on cytological diagnosis). Of the 55 patients experiencing resolution, 19 had clinical fibro-adenoma (12 by FNAC) and 36 had discrete fibro-adenosis.

At the 2-year review clinic 64 women re-attended. Another 3 had experienced resolution of their lump, 1 had grown a new fibro-adenoma in the opposite breast, and 23 had lesions unchanged from their time of original discharge (15 with fibro-adenoma, and 8 with discrete fibro-adenosis, both clinically and cytologically diagnosed). Only two women experienced periodic appearance of their original lesions.

The mean age of those with fibro-adenoma was 28·2 ± 9·8 years, and with discrete fibro-adenosis was 32·5 ± 11·5 years (no significant difference). There was no difference in the age of patients electing for excision or being advised to have their lumps removed (35·6 ± 12·1 *versus* 39·5 ± 7·2 years) or between those with lesions present at discharge and those with resolution

Discussion

This study addresses two problems in the management of benign breast disease—can a lump be safely left *in situ*, and what happens to such lesions?

We have shown that a proportion (49 per cent) of discrete

Table 4 *Details of patients* experiencing resolution of their lumps*

	No. of patients	Diagnosis
Lump present at discharge	26 (32)†	14 Fibro-adenoma, clinically diagnosed 12 Discrete fibro-adenosis, clinically diagnosed (all fibro-epithelial hyperplasia)
Lump resolved	55 (68)‡	19 Fibro-adenoma, clinically diagnosed (12 cytologically diagnosed) 36 Discrete fibro-adenosis

Percentages are given in parentheses; * 81 patients were followed for > 2 years, † 23 per cent and ‡ 49 per cent of the original study group of 112 patients benign breast lumps can be expected to resolve with time. This study recruited patients with discrete disease and not those with diffuse upper outer quadrant lumpiness, which is well known to vary in size. Clinical experience tells us that some young women with diffuse fibro-adenosis will experience resolution. The fibro-adenoma is uncommon after the third decade, and it is unlikely that all have been seen and excised. Post-mortem studies have shown that fibro-adenomas are unusual in the elderly[13]; only 4 of 225 patients (1·8 per cent) studied had obvious fibro-adenomas, of whom 2 were in the 40–49 age group, 1 in the 50–59 and 1 in the 80–89 age groups.

The mechanism of resolution histologically is based on merging of the lump into the surrounding stroma and hyalinization[14]. Studies following the course of fibro-adenomas are rare, but one published in Australia showed that 2 out of 17 such lesions resolved[15] In our series a higher proportion was seen to disappear. Even if we restrict analysis to the 32 fibro-adenomas diagnosed clinically and confirmed cytologically, there is still a 59 per cent resolution rate (*Table 4*).

FNAC has high sensitivity and specificity in the diagnosis of malignant disease, and absence of malignant cells allows a diagnosis of the benign lump. No patients with breast carcinoma have been seen in those with a lump diagnosed cytologically as benign, although four cases diagnosed clinically as benign were shown to be cancers by cytology Two of these patients were older than the mean age of the fibro-adenoma group, and all had rarer subtypes of cancer.

A study such as this is dependent on the skill of a cytopathologist with a special interest and expertise in breast disease Reporting in the clinic is an added refinement, allowing repetition of unsatisfactory specimens The concordance between immediate reporting using the best slide and later reports using all the remaining slides is good[10].

It is hard to assess the risk of malignancy developing in a fibro-adenoma, but it must be low; a case has recently been reported[16]. Haagensen[17] examined the previous reports of such an association and finds them unproven. He found two cases of lobular neoplasia within a fibro-adenoma, but no case of adenocarcinoma arising exclusively within a fibro-adenoma in his large series.

This study demonstrates the resolution of discrete benign breast lesions and that patients may be safely offered conservative, non-surgical treatment in the expectation of resolution in half the cases.

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Temperature gradient between the rectum and the anal canal: evidence against the role of temperature sensation as a sensory modality in the anal canal of normal subjects

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Temperature difference between the rectum and anal canal is a fundamental requirement for the hypothesis that temperature sensation is of physiological importance in discrimination of anorectal contents occurring during the 'sampling reflex'. The temperature gradient between the rectum and the anal canal was measured in 47 normal subjects (mean age 51·6 years ± 16·8 s.d., 24 men). The maximum mean difference in temperature between the rectum and the anal canal was 0·13°C (0·06–0·19, 95 per cent confidence intervals) and occurred 4 cm from the anal verge. This difference is too small to be detected by the anal canal mucosa. Under normal physiological circumstances the conscious appreciation of temperature of faeces passing from the rectum to the anal canal is impossible during the anorectal sampling reflex.

Keywords: Anorectal sensation, temperature

It has been suggested that decreased awareness of temperature in the anal canal is important in the pathogenesis of faecal incontinence, and that temperature sensation may aid discrimination between gas, liquid and solid, and is an important sensory modality in the normal mechanism of continence[1]. Although awareness of change in temperature exists in the anal canal[1], there is no support for the hypothesis that under normal physiological conditions temperature discrimination occurs there. If temperature sensation is important in the mechanism of continence it would be activated when faeces descend from the rectum into the anal canal, as part of the sampling reflex[2,3]. The temperature of the faeces must be different from that of the adjacent mucosa in order to create a temperature gradient across the interface, for heat transfer to occur, and for consequent stimulation of temperature receptors[4]. As faecal transit in the distal colon and rectum is slow except during defaecation, it is reasonable to assume that the temperature of faeces will have equilibrated with that of the rectum. Thus the fundamental requirements for the hypothesis that temperature sensibility is important in the anal canal are, firstly, the presence of a temperature gradient between the rectum and anal canal and, secondly, that the magnitude of the gradient exceeds the minimal detectable temperature difference.

The aim of this study was to measure the temperature gradient between the rectum and anal canal of normal subjects and to review the above hypothesis in the light of experimental results

Patients and methods

Forty-seven normal subjects, mean age 51·6 years ± 16·8 s d (24 men), were studied. They were all volunteers with no history of local anorectal disorders

All subjects were studied in the left lateral position without prior bowel preparation or clinical examination. Temperature was measured using an electronic thermometer (Waeschel DS 77, JBC, UK) consisting of a thermocouple (4 mm diameter) mounted on a semirigid probe 8 cm long. The probe was inserted up to 7 cm into the anal canal, at 1 cm stations. The temperature at each station was measured. Temperature measurements were also made at 1 cm stations while withdrawing the probe

The electronic thermometer gives a reading only when in thermal equilibrium with its surroundings, and was validated against a reference mercury and glass thermometer (BDH model no 601) graduated in 0 05°C intervals over a temperature range of 35–38°C by immersion in a water bath

Additionally, in 11 subjects, mucosal electrosensitivity[5,6] was measured after the temperature recordings had been made at the same 1 cm stations up to 7 cm, to confirm that the probe was of sufficient length to traverse the entire anal canal and enter the rectum, and to measure the length of anal canal lined by sensory mucosa. The normal anal canal mucosa is very sensitive to this stimulus, and the rectal mucosa is insensitive.

Results

Validation of thermocouple

Results of validation of the electronic thermometer against the reference thermometer over a temperature range of 35–38°C showed a consistent bias of −0·07°C (from −0 05 to −0 09, 95 per cent confidence intervals), and repeatability coefficient[7] of 0·05°C The precision of the electronic thermometer over the range of temperatures encountered in normals is shown in *Figure 1*

Length of anal canal

The mean anal canal length was found to be 4 cm ± 0·9 by mucosal electrosensitivity. This is consistent with the anal canal length of normals, as estimated by manometry in an earlier study[6].

Temperature gradient

The mean temperature at each station during insertion of the probe was higher than on withdrawal due to heat loss to the thermocouple (*Figure 2*). Repeatability for the temperature differences measured on insertion *versus* those on withdrawal of the probe was: mean difference, 0 01°C ± 0·02; repeatability coefficient, 0·06°C.

Figure 3 shows the mean temperature and 95 per cent confidence intervals at each station on insertion of the probe from 1 to 7 cm from the anal verge. The data show a clear temperature gradient from the rectum to the anal verge. It is interesting that the mean temperature of the rectum is lower than that of the anal canal, except for the most distal part, 1 cm from the anal verge

Figure 4 shows the mean difference in temperature at each 1 cm station from the rectum at 7 cm to the anal verge. The

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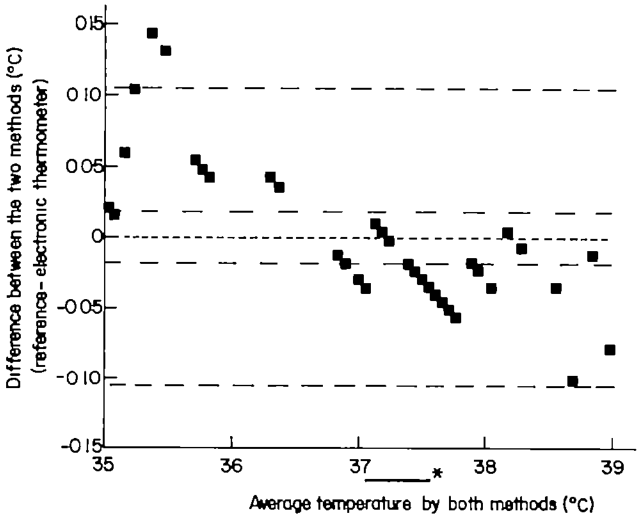

Figure 1 *Results of validation of electronic thermometer (bias corrected). ———, Upper and lower limits (±2 s d.) of the agreement, – – 95 per cent confidence interval, * range of temperature measured in anal canal*

maximum mean difference between rectum and anal canal was at 4 cm and amounts to 0·13°C (0·06–0·19, 95 per cent confidence intervals).

Calculation of the incremental gradient, or mean temperature change/cm (*Figure 5*), showed that the maximum mean difference/cm, 0·06°C (0·02–0·1, 95 per cent confidence intervals), occurred between 6 cm and 5 cm from the anal verge.

Discussion

The results of validation of the thermocouple showed a consistent negative bias for absolute temperature against the reference thermometer, and the actual temperature at each station was calculated by subtraction of this bias. For the measurement of temperature gradients, which are independent of the bias, the thermocouple was accurate with a precision, demonstrated by 95 per cent confidence intervals, of ±0·02°C and a repeatability of 0·05°C. Measurements of mucosal electrosensitivity gave a mean anal canal length of 4 cm ± 0·9, which shows that the thermometer was long enough to traverse the anal canal and reach the rectum, and that sensitive anal mucosa lined only the lower 4 cm of the canal.

The mean temperature at each station on insertion of the probe was higher than on withdrawal because of heat loss to

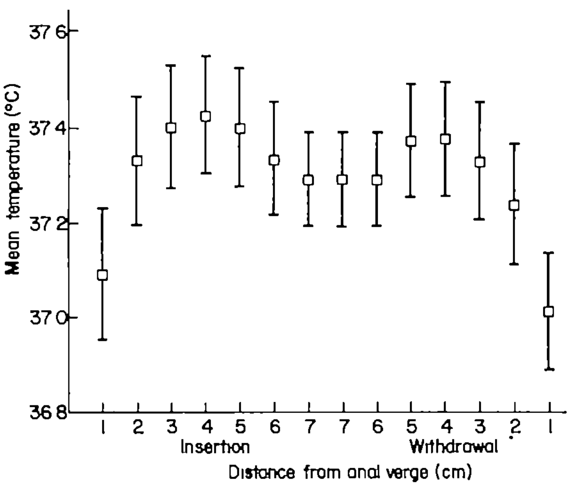

Figure 2 *Mean temperature (and 95 per cent confidence intervals) at each 1 cm station during insertion and withdrawal*

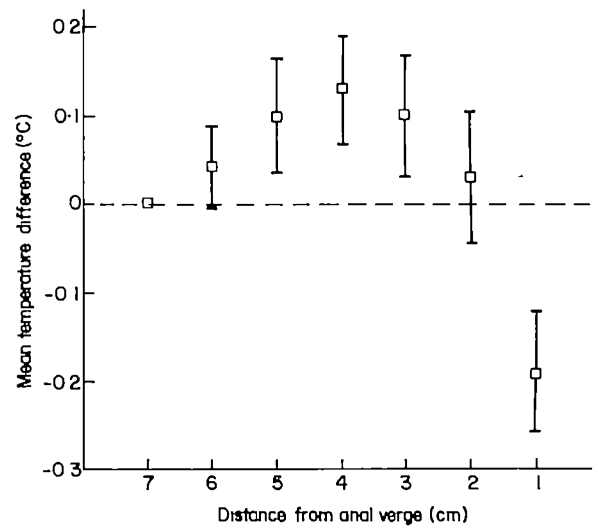

Figure 4 *Mean difference in temperature (and 95 per cent confidence intervals) from rectum (7 cm) at each 1 cm station*

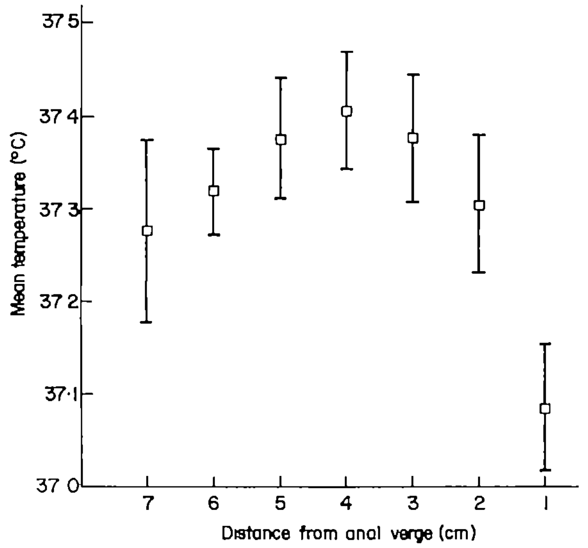

Figure 3 *Mean temperature (and 95 per cent confidence intervals) at each station on insertion*

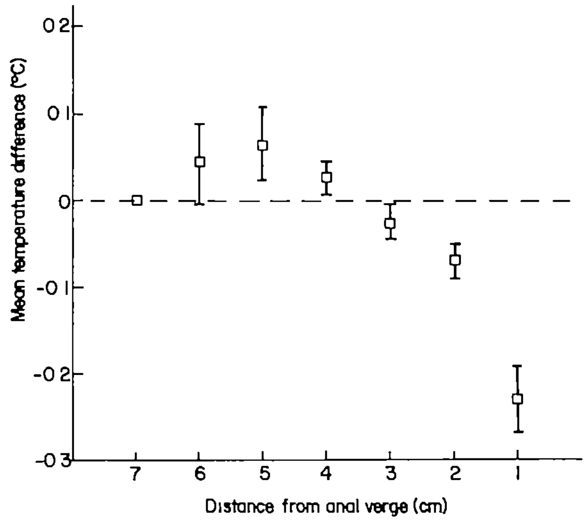

Figure 5 *Mean change in temperature per centimetre (and 95 per cent confidence intervals) at each station from rectum to anal verge*

the thermocouple. However, the temperature differences measured on insertion *versus* those on withdrawal of the probe were similar, showing that the temperature differences between stations were maintained.

The results show a clear temperature gradient from the rectum to the anal verge, and it is interesting that the mean temperature of the rectum is lower than that of the anal canal, except for the lowest 1 cm from the anal verge. The reason for this temperature difference is probably due to the increased blood flow in or adjacent to the anal mucosa through the arterioles of the anal cushions and the apposition of the mucosa maintained by the sphincter musculature, which also generates heat as a consequence of tonic activity.

For the purpose of testing the hypothesis, the lowest 1 cm may be ignored, because the normal sampling reflex does not allow faeces to descend to this level and therefore results between 2 and 7 cm from the anal verge only need be considered. The maximum mean temperature difference between rectum and anal canal was at 4 cm and amounted to 0·13°C (0·06–0·19, 95 per cent confidence intervals), and the maximum mean difference per centimetre was 0·06°C (0·02–0·1, 95 per cent confidence intervals) and occurred between 5 and 6 cm.

In contrast to the rectum, the anal canal is densely supplied by sensory nerve endings and carries modalities of touch, pain, movement, and temperature for cold and heat[8]. The upper part of the anal canal is able to 'sample' the contents of the lower rectum, and may allow sensory discrimination of the contents[2]. The length of anal canal mucosa available for sampling has been estimated at 0·8 cm (range 0·1–2·0)[2] from the upper part of the anal canal to approximately 3 cm from the anal verge. Quantitative assessment of sensation of the anal canal has shown this area to be particularly sensitive to electrostimulation[5,6]. In the first quantitative assessment of temperature sensation in the anal canal Miller *et al.*[1] reported that this part of the anal canal could detect changes in temperature of as little as 0·8°C (lowest median) and confirmed this in a later study (median 0·9°C, range 0·8–1·3)[3].

For temperature sensation to play a role in the sensory discrimination of the anal canal under normal physiological conditions, the anal canal must be able to sample faeces from the rectum and bring them into contact with the temperature sensitive mucosa. In addition, the temperature of the faeces must be sufficiently different to create a temperature gradient larger than the minimal detectable temperature change between them and the mucosa with which they are in contact.

The results of this study show that the largest temperature gradient between the rectum and the part of the anal canal involved in the sampling reflex was 0·13°C with 95 per cent confidence intervals of 0·06–0·19°C. This is clearly subthreshold for conscious appreciation of temperature change as described by Miller *et al.*[1].

The data show that under normal physiological circumstances the conscious appreciation of the temperature of faeces passing from the rectum to the anal canal is impossible during the anorectal sampling reflex.

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Faecal incontinence associated with reduced pelvic sensation

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Eight patients with faecal incontinence associated with high threshold of rectal sensation are described. All had a normal anal sphincter on clinical and physiological assessment including anal manometry, pudendal nerve latency estimation and single fibre electromyography. In each case however rectal sensation was abnormal. The threshold of rectal sensation was 143 ± 33 ml (range 110–200 ml) compared with control values of 39 ± 14 ml (range 25–65 ml) ($P < 0.005$) *in 12 normal age-matched individuals. The degree of rectal distension required to initiate the recto-anal reflex was no different in the incontinent patients (19 ml, range 15–25 ml, compared with 22 ml, range 15–30 ml, in the controls). There was also no difference in the maximal tolerated volume of rectal distension between the groups (291 ± 87 ml and 279 ± 91 ml respectively). These observations may have defined a small group of patients with incontinence in whom an abnormality of rectal sensation rather than sphincter incompetence could be a part of the pathophysiological disorder.*

Keywords: Anal sphincter, faecal incontinence, sensation

Faecal incontinence has an estimated prevalence in the community overall of 4·2 per 1000 and >10 per 1000 in the population aged over 65 years[1]. In most cases evidence of damage to the pelvic nerves which innervate the muscles of the pelvic floor and anal sphincter can be demonstrated on physiological testing[2–8] Minor incontinence may also be caused by local anorectal conditions[9] which may be traumatic or due to inflammatory, neoplastic or congenital diseases. In this paper we report a group of patients with faecal incontinence without any local anorectal abnormality, somatic pelvic nerve damage or sphincter weakness

Patients and methods

Between January 1986 and April 1987 eight patients with minor incontinence and no local anorectal condition or anal sphincter weakness were seen Each patient had a minor faecal leak requiring the use of a pad. There were seven men and one woman, with a mean age of 48 years (range 23–66 years) One patient had intermittent excessive straining at stool while the remainder had a normal defaecatory pattern None had incontinence associated with diarrhoea or pain as can occur in the irritable bowel syndrome[10,11] No patient had haemorrhoidal or rectal prolapse One patient had undergone haemorrhoidectomy 6 years previously and another had had injection of haemorrhoids 17 years previously. The former had a 1-year history of incontinence and the latter had been symptomatic for 6 months and also suffered severe pruritis ani The onset of incontinence therefore postdated haemorrhoidectomy by several years in both patients. None of the patients was diabetic or had neurological disease

Each patient underwent proctosigmoidoscopy after digital examination None was found to have any evidence of anorectal disease In particular there was no fissure, fistula, haemorrhoids or mucosal prolapse and in each case the anal sphincter and pelvic floor were normal on digital examination. Anal manometry, measurement of rectal (pelvic) sensation, perineal descent and pudendal nerve terminal motor latency, and single fibre electromyography were carried out on each patient. No patient had faecal loading at the time of testing

Twelve patients without anorectal disease, having colonoscopic follow-up for polyps or surgery not related to the anorectum, were used as control subjects There were nine men and three women, mean age 43 years (range 21–67 years). Each patient had anal manometry and measurement of rectal sensation

Anorectal manometry

Anal manometry was carried out using a closed water-filled system with a micro-balloon connected by a stiff polyethylene tube to a pressure transducer and recording apparatus The maximal anal canal pressure at rest and the maximal increase during voluntary contraction, and the anal canal length were measured The recto-anal reflex was tested by placing a 5 cm latex balloon in the rectum with its distal end 5–6 cm above the anal verge. The balloon was inflated with air in 10 ml increments while simultaneously recording anal pressure. The minimum volume required to induce anal sphincter relaxation of 20 cmH_2O or more was recorded and called the threshold volume initiating the recto-anal reflex.

Rectal sensation

The rectal balloon was then inflated with air in increments of 50 ml every 15 s until its presence was perceived by the patient. This volume was recorded and called the threshold of rectal sensation The maximum tolerable volume was measured by continuing the inflation to a point which produced pain or marked pelvic discomfort.

Pudendal nerve terminal motor latency

The pudendal nerve terminal motor latency (PNTML) was measured as previously described[3,5,12]. The pudendal nerves were stimulated transrectally using a rubber finger stall Square wave supra-maximal stimuli were delivered to the nerves at the level of the ischial spines and the compound muscle action potentials evoked in the external anal sphincter were displayed on the oscilloscope screen and recorded on the paper printout of the electromyography (EMG) apparatus (Neuromatic 2000, Dantec, Denmark) The mean PNTML in normal subjects is 2·0 ± 0·2 ms (s.d.)[3,13]

Perineal descent

The position of the perineum was measured with respect to the plane of the ischial tuberosities at rest and during a defaecation straining effort[14]. The position is considered to be abnormal if it lies more than 1 cm below the level of the ischial tuberosities during a maximal straining attempt[14]

Single fibre electromyography

Single fibre EMG was carried out as previously described[4] and the fibre density in the external anal sphincter calculated. The fibre density in normal subjects is 1·5 ± 0·1 (References 4 and 13)

Statistical analyses

The two sample t test was used in the comparison of mean values in the incontinent and control groups Variance is expressed as standard deviation throughout

Results

The mean resting anal canal pressure in the incontinent group (96 ± 21 cmH_2O, range 60–130 cmH_2O) was higher than in the

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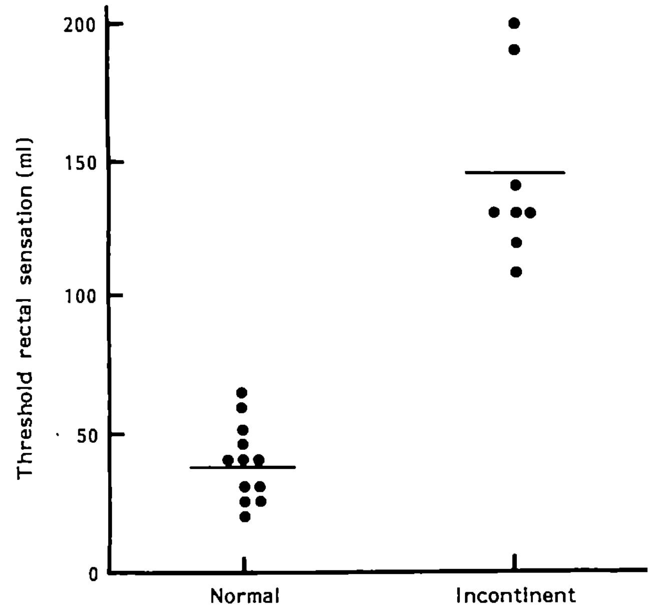

Figure 1 *Threshold of rectal sensation in incontinent and normal control subjects* (P<0·005)

control group (71 ± 14 cmH_2O; $P < 0{\cdot}005$). The mean anal canal pressure on maximal voluntary contraction in the incontinent and control groups was 143 ± 93 cmH_2O and 103 ± 35 cmH_2O respectively (n.s.). The mean anal canal length in the incontinent and control groups was 3·4 cm (range 2·5–4·5 cm) and 3·5 cm (range 2·5–5 cm) respectively (n.s.). The recto-anal reflex was present in each patient. The mean threshold volume initiating the recto-anal reflex in the incontinent group was 19 ml (range 15–25 ml) and 22 ml (range 15–30 ml) (n.s.) in the control group

The position of the perineum at rest in the incontinent and control groups was 1·6 ± 0·4 cm and 1·8 ± 0·5 cm above the transischial line respectively (n.s.), and 0·7 ± 0·8 cm and 1·3 ± 0·7 cm above this line respectively during straining (n.s.).

The PNTML was normal in each incontinent patient (mean PNTML 1·9 ± 0·2 ms, range 1·6–2·3 ms), as was the fibre density (mean 1·38 ± 0·13, range 1·2–1·6).

The mean threshold of rectal sensation in the incontinent group was 143 ± 33 ml (range 110–200 ml) and in the controls 39 ± 14 (range 25–65 ml) ($P < 0{\cdot}005$) (*Figure 1*). The mean difference between the threshold of rectal sensation and threshold of the recto-anal reflex in the incontinent and control groups was 125 ml and 17 ml respectively ($P < 0{\cdot}005$) (*Figure 2*). The mean maximum tolerable volume in the incontinent and control groups was 291 ± 87 ml and 279 ± 91 ml respectively (n.s.).

Discussion

The mechanism of faecal continence is a complex process involving integrated control of the anal sphincter and pelvic floor muscles. This is largely an unconscious process controlled by spinal[15] and local nerve pathways[16], but is also regulated by the conscious will. The anorectal angle and the pressure zone generated by the internal and external anal sphincters are critical factors but pelvic sensory input[17] and anal sampling[18] may also be important. Faecal incontinence may occur in the presence of a normal anal sphincter and pelvic floor muscles. Thus faecal impaction with severe chronic constipation may result in faecal leakage[9]. In the presence of diarrhoea the normal anal sphincter may be unable to retain large volumes of watery stool[9]. None of these factors was present in our patients.

The patients presented in this series had neither a local anal condition, nor pudendal nerve damage as shown by normal PNTML and fibre density values in the external anal sphincter to explain their faecal incontinence. Although one patient had abnormal perineal descent on straining, anal pressures were normal as they were in the remaining eight.

The presence of flatus or stool in the rectum is perceived as a distinct sensation of pelvic 'fullness'. This may be simulated by distension of the rectum with an air- or water-filled balloon. It has been suggested that the receptors responsible for this sensation may reside in the muscles of the pelvic floor rather than in the rectal wall[19]. Stretch receptors have been observed in the levator muscles[20], and muscle spindles have been identified in the external anal sphincter[21] and puborectalis[22]. In each of the patients in this study there was an elevated rectal sensitivity threshold and the mean threshold of sensation was significantly higher than in the control group Reported values of the threshold of rectal sensation vary widely[23,24]. It is not influenced by age or sex in normal subjects[23,25], and the observed differences in threshold probably reflect differences in the technique of measurement, particularly in the rate of inflation of the rectal balloon.

The mechanism for the sensory loss observed in this study is unknown. Raised rectal sensitivity threshold has been observed in children with faecal soiling[26] and adults with diabetes mellitus and faecal incontinence[27]. Similarly an increase in sensitivity threshold has been reported in chronic childhood constipation[26,28] and in adults with faecal impaction and incontinence[29]. However other studies on patients with chronic constipation have found normal sensory threshold values in children[30] and adults[31], and a normal sensory threshold but a raised threshold of the urge to defaecate[24].

Molnar *et al.*[26] found that in children the thresholds of rectal sensation and complete internal sphincter relaxation were nearly the same. In the present study the threshold of rectal sensation was at least 90 ml greater than the threshold of the recto-anal reflex in each patient. While the two parameters were not measured during the same experimental procedure others have also measured the thresholds in this way[28,29], and the large difference between the two values in the patients compared

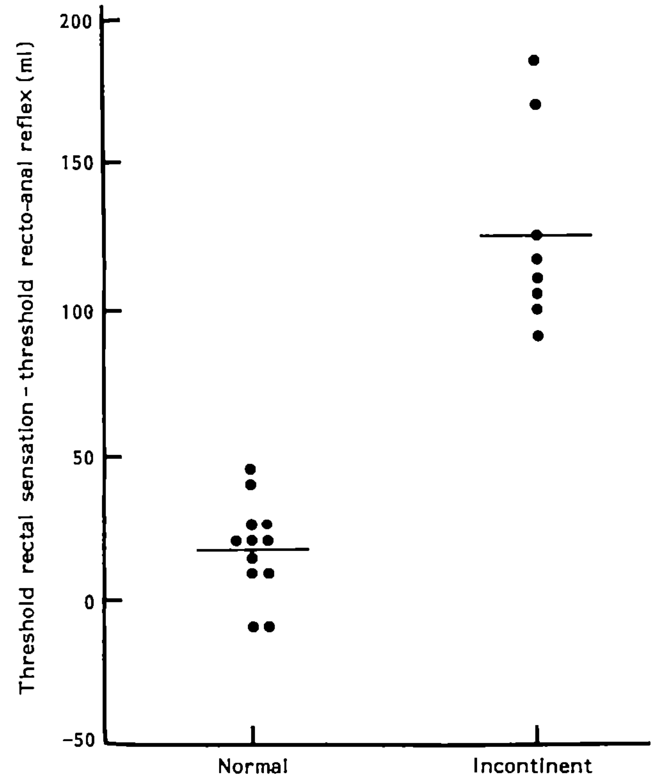

Figure 2 *Difference between the threshold of rectal sensation and threshold of the recto-anal reflex in incontinent and normal control subjects* (P < 0 005)

with the controls would appear to be significant. Nevertheless the functional importance of the relation between the threshold of sensation and the threshold of the recto-anal reflex remains uncertain, but internal anal sphincter relaxation without an awareness of rectal distension could explain the minor incontinence suffered by the patients in this study. It is of interest that most were men and none was older than 66 years. Both of these features are atypical of patients with pudendal neuropathy and the patients described here may exemplify a distinct and separate clinical entity characterized by a disorder of rectal sensation.

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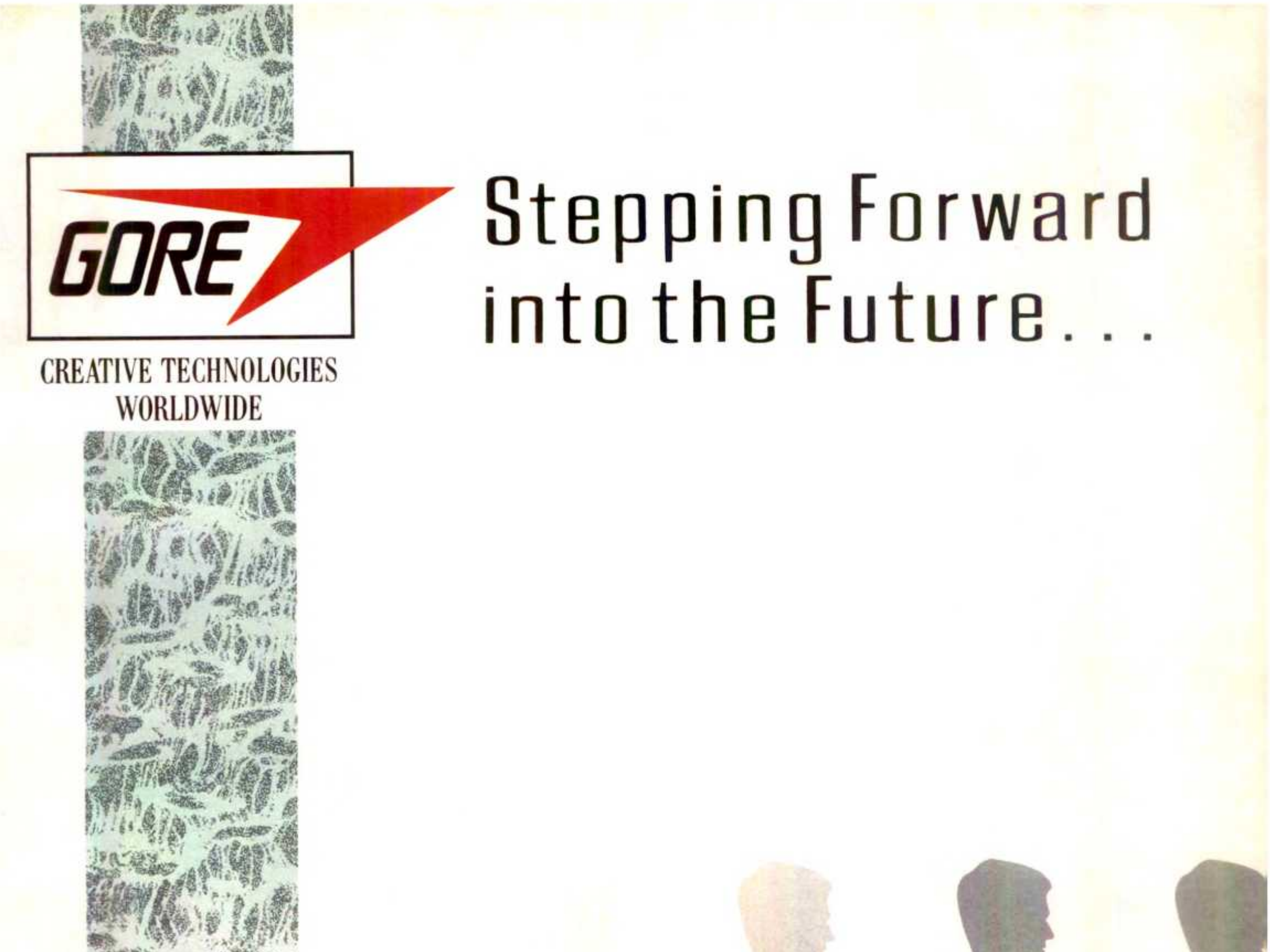
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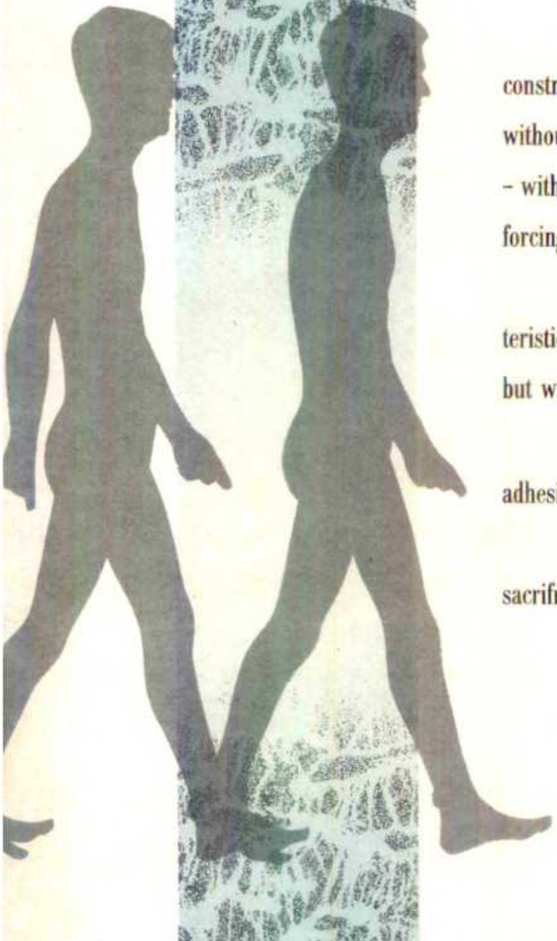

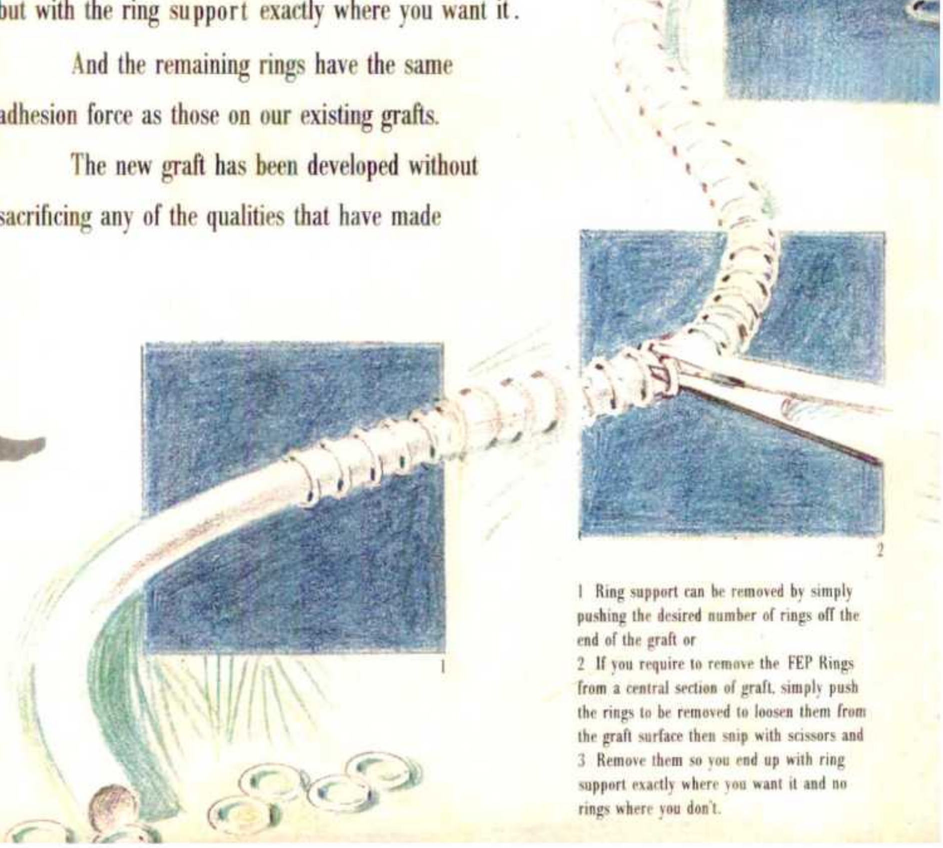

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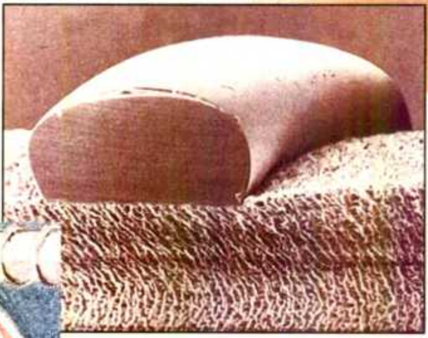

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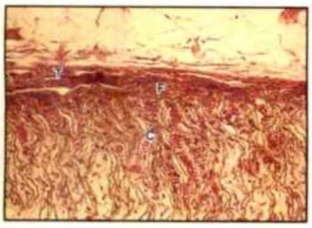

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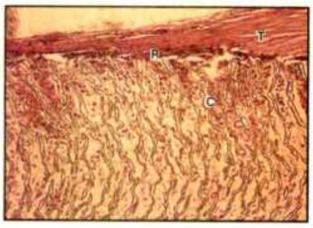
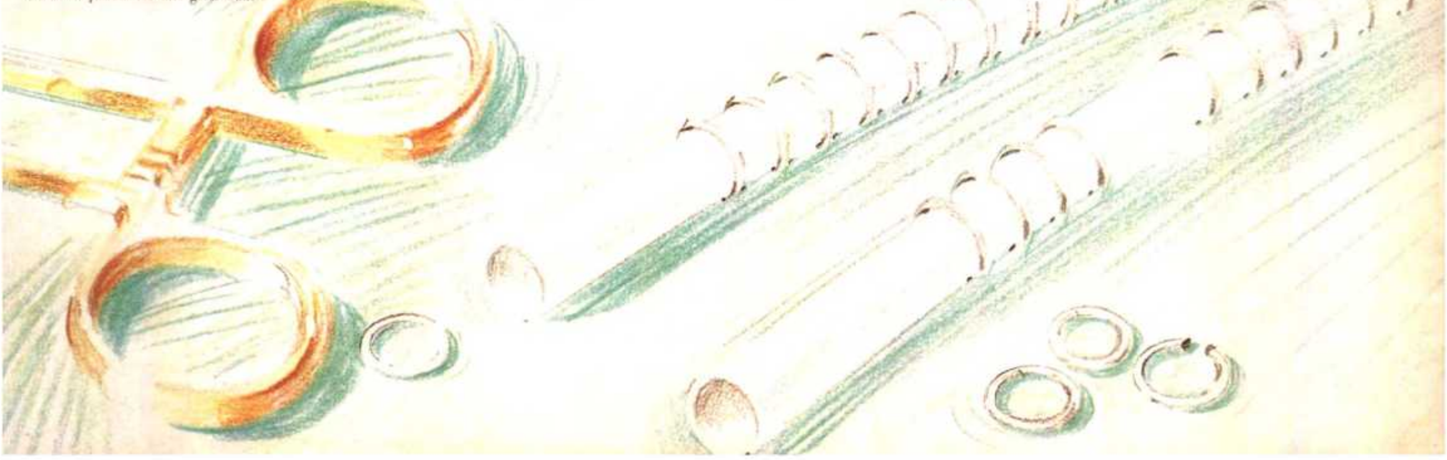


Outer surface, GORE-TEX® Vascular Graft.
H & E 50 X Canine 77 days
Tissue (T) attached to reinforcing film (R). Cells (C) have penetrated into graft wall.



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Paget's disease of the anal margin

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A follow-up study of 22 patients with Paget's disease of the anal margin was conducted to determine the prevalence of invasive disease and coexisting visceral carcinomas, cure and survival rates. Seventy-three per cent of the patients suffered from persistent pruritus ani. Seven (32 per cent) patients had malignancy (invasive Paget's disease ($n = 5$) *and coexisting visceral carcinoma* ($n = 2$)) *and six (27 per cent) developed malignancy (invasive Paget's disease* ($n = 4$) *and coexisting visceral carcinoma* ($n = 2$)) *during follow-up, giving an overall occurrence of malignancies of 59 per cent (95 per cent confidence limits: 36–79). The median follow-up period was 9 (range 0·5–25) years. No difference in length of history could be found between patients with or without malignancy. The estimated cure rate by actuarial analysis among radically treated patients was 64 per cent (95 per cent confidence limits: 43–91) at 1 year and 45 per cent (95 per cent confidence limits: 18–72) at 8 years after primary treatment. The 5- and 10-year crude survival rates of 54 per cent and 45 per cent, respectively, were significantly lower than the corresponding values of 84 per cent and 60 per cent for the normal population* ($P < 0{\cdot}01$). *Patients with persistent pruritus ani and a perianal skin lesion should be biopsied frequently. If Paget's disease is diagnosed, physical examination of the patient and anorectal region must be done carefully and repeatedly.*

Keywords: Paget's disease, anal margin

Paget's disease of the anal margin is histologically identical to Paget's disease of the breast[1]. The lesion is defined as an intra-epidermal neoplasm[2]. The epidermis is infiltrated by irregular large pale cells, scattered between compressed squamous epithelial cells of otherwise normal appearance. The lesion may be accompanied by an invasive adenocarcinoma or an *in situ* adenocarcinoma of the apocrine glands. Patients with Paget's disease may also have or develop a coexisting visceral carcinoma more frequently than the normal population[2].

Paget's disease of the anal margin seems to be an extremely rare condition as less than 50 cases have been reported in the literature and most have appeared as case reports[3–6]. Therefore, it is not possible to estimate the true incidence of Paget's disease or the frequency with which Paget's disease of the anal margin becomes clinically malignant or coexists with a visceral carcinoma.

To subject this problem to critical examination a long-term follow-up study of the clinical course of 22 patients with Paget's disease of the anal margin was performed.

Patients and methods

Records of all patients with Paget's disease of the anal margin coded between 1953 and 1982 were reviewed (see below). Criteria for inclusion in the study were as follows: (1) the first treatment of the lesion was undertaken in the period under review; (2) all diagnoses were confirmed histologically; and (3) patients who had only Paget's disease of the anal margin were enrolled in the study. Patients with extensive vulvar disease that also included the anal margin were not included.

For inclusion in the study, histological sections of biopsies had to demonstrate vacuolated Paget cells within the epidermis. The Paget cells were more numerous at the tips and margins of the rete ridges. The pilary outer root sheath, sebaceous glands, and apocrine sweat gland structures were carefully examined for content of Paget cells. Carcinoma *in situ* was considered to be present if apocrine structures showed Paget cells confined by intact basement membrane. Apocrine structures showing a proliferation of Paget cells, basement membrane disruption and similar cells in the surrounding stroma were interpreted as invasive adenocarcinoma (invasive Paget's disease of the anal margin).

Paget's disease of the anal margin was distinguished from malignant melanoma, Bowen's disease, X-ray keratosis, squamous cell carcinoma and leucoplakia on the basis of a positive aldehyde-fuchsine (pH 1·7) reaction of the Paget cells.

The anal margin was defined as a circle of 6 cm centred on the anus.

Twenty-two patients met these requirements. None of the patients was lost to follow-up. The median follow-up was 9 (range 0·5–25) years. The median age was 70 (range 48–83) years. Thirteen of the patients were women (59 per cent).

The patients were traced during a follow-up investigation of 261 patients treated for malignant tumours of the anus in Denmark between 1943 and 1974 as previously described from card files of the Department of Surgical Gastroenterology C, Rigshospitalet, Copenhagen; Institute of Pathology, Sundby Hospital; and Laboratory of Pathology, Kastrup, Denmark[7,8]. The laboratory receives specimens from practising dermatologists and surgeons, and not from hospitals. Eleven of the patients were primarily treated as outpatients by a practising surgeon or dermatologist.

In February 1987, the records were obtained from the different hospitals and physicians and were reviewed. The patients were traced in the Danish Central Person Register. If patients had died, the dates and causes of death were available from the National Board of Health, which obtains all death certificates issued since 1943. Information about control examinations, detection of recurrent disease and secondary treatment were obtained from records and general practitioners. Each patient had a follow-up investigation to death or to current status in 1987.

Recurrence rates were estimated by the actuarial method with 95 per cent confidence limits according to Greenwood's estimate[9]. When a percentage statement is used, 95 per cent confidence limits are given in brackets. Survival curves were based on life-table analysis. 'Time zero' for the survival analysis was defined as the time of diagnosis of Paget's disease of the anal margin. Differences in survival curves were estimated by the log rank test[10]. P values of less than 0·05 were considered significant.

Results

Primary histological diagnosis

In three patients the lesion was totally removed primarily while 19 patients only had a biopsy of the lesion and subsequently

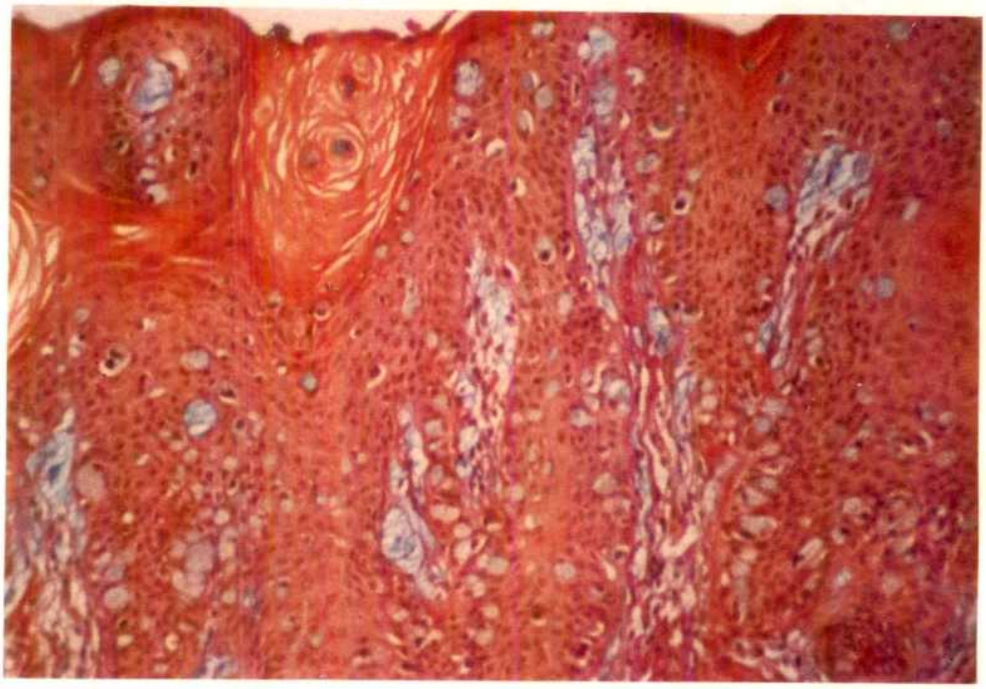

Figure 1 *Paget's disease of the anal margin. The section shows numerous vacuolated Paget cells within the upper part of the epidermis. No Paget cells are demonstrated in apocrine structures. The Paget cells are numerous along the ridges and tips of the rete ridges. Some of the cell nuclei are compressed by an abundant basophilic staining mucinous material in the cytoplasm. The vacuolated cells do not show evidence of malignant dyskeratosis. (Alcian blue stain × 125)*

Table 1 *Various types of primary treatment in 22 patients with Paget's disease of the anal margin (PAM) with or without invasion or* in situ *changes of apocrine structures*

Primary treatment	Invasive PAM ($n=5$)	*In situ* PAM ($n=4$)	PAM alone ($n=13$)	No. of radical procedures	No. of recurrences (%)
Curettage	0	0	5	5	5 (100%)
Local excision	1	1	8	10	4 (40%)
Abdominoperineal resection	3*	2†	0	1	0
Radiotherapy	1	1	0	2	2 (100%)

* Two patients with coexisting visceral carcinoma (adenocarcinomas of the rectum); † two patients with coexisting visceral carcinoma (squamous cell carcinoma of the anal canal and adenocarcinoma of the rectum)

underwent total excision or curettage of the lesion. Histological examination with serial sections showed invasive Paget's disease of the anal margin in 5 patients (23 per cent), *in situ* changes in 4 patients (18 per cent) and Paget's disease without involvement of the pilar outer root sheath or the apocrine glands in 13 patients (59 per cent).

Figure 1 demonstrates the typical histological features of Paget's disease of the anal margin without invasion or *in situ* changes in the apocrine gland structures. The photomicrograph shows the upper part of the epidermis infiltrated by irregular pale cells (Paget cells).

Coexisting visceral carcinomas

Two of the five patients with malignant Paget's disease of the anal margin had a coexisting carcinoma of the rectum diagnosed at the same time as their anal disease, and two of the four patients with *in situ* changes also had coexisting visceral carcinoma diagnosed (adenocarcinoma of the rectum in one patient and squamous cell carcinoma of the anal canal in the other) besides their Paget's disease. All of these patients, except the patient with coexisting squamous cell carcinoma of the anal canal, also had distant metastases (lung and liver) at the time of diagnosis.

Two of the three patients with invasive Paget's disease of the anal margin and no coexisting visceral carcinoma had distant metastases (liver, bone) from the invasive Paget's disease diagnosed at the time of diagnosis of Paget's disease.

Localization and size

In seven cases (32 per cent), the lesion was located circumferentially around the anus, whereas in 15 cases (68 per cent) the lesion was well-defined although of varying size and appearance. Ten of these cases were located laterally to the anus, three posteriorly and two anteriorly. The median size of the 15 lesions was 3 (range 2–15) cm.

Symptomatology

The symptoms encountered were: moderate to severe pruritus ani (73 per cent), bleeding (55 per cent), feeling of a lump (41 per cent), perianal soiling (41 per cent) and changed bowel habit (32 per cent). The median duration of symptoms before appropriate treatment was initiated was 18 (range 3–48) months for patients with invasive Paget's disease of the anal margin, 20 (range 2–40) months for patients with *in situ* changes, and 20 (range 4–42) months for Paget's disease of the anal margin without invasion or *in situ* changes. One of the reasons for the delay in instituting appropriate treatment was that an erroneous diagnosis was made at first physician visit (atopic eczema in 73 per cent, lichen sclerosis et atrophicus in 18 per cent, condylomata acuminata in 4 per cent and hyperkeratosis in 4 per cent.

Treatment

The different types of primary treatment of patients with the different Paget's diseases of the anal margin with or without coexisting visceral malignancies are shown in *Table 1*. In all, 18 patients were considered to have been radically treated including 1 patient with invasive Paget's disease of the anal margin who was treated by wide local excision. The skin was excised for at least 1 cm beyond the tumour and excision was carried as far as the sphincter deep to the tumour.

Five patients with Paget's disease of the anal margin without invasion or *in situ* changes were primarily treated by curettage by dermatologists and all were considered radically treated. All of these patients had small tumours (<3 cm). Two patients were treated by radiotherapy; one with an invasive Paget's disease of the anal margin (3000 cGy) and one with *in situ* changes (5000 cGy). All patients treated by curettage or radiotherapy developed recurrent disease within 6 months.

Abdominoperineal resection was performed in five patients. However, four of these had distant metastases at the time of operation and were not cured. One patient with *in situ* Paget's disease of the anal margin and a coexisting squamous cell carcinoma of the anus was cured by abdominoperineal resection and was alive 8 years later free of disease.

One patient with invasive Paget's disease of the anal margin was treated by local excision and was cured and free of disease 9 years later.

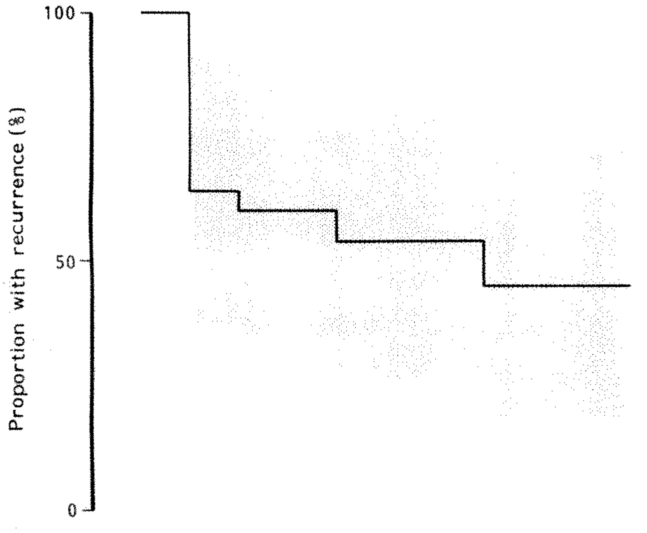

Figure 2 *Estimated cure rates after actuarial analysis (95 per cent confidence limits according to Greenwood's estimate) for patients with Paget's disease of the anal margin*

Cure rate

Figure 2 shows the cure rate as estimated by actuarial analysis. After 5 years the cure rate was 54 per cent (95 per cent confidence limits: 26–81) and after 8 and 10 years it was 45 per cent (95 per cent confidence limits: 18–71). The latest recurrence occurred 8 years after primary treatment.

Four recurrences developed into invasive Paget's disease of the anal margin from previously non-invasive lesions or lesions thought not to be *in situ* forms.

Of the 11 recurrences, 5 developed into non-*in situ* forms of Paget's disease of the anal margin from previously non-invasive lesions or lesions thought not to be *in situ* forms. Two of these patients had a coexisting visceral adenocarcinoma diagnosed (rectum; colon) together with the recurrent Paget lesion.

Two recurrences were without invasive or *in situ* signs and both recurrences developed from lesions previously thought to be *in situ* forms of Paget's disease of the anal margin.

Secondary treatment

Table 2 shows the secondary treatment given to the patients. The treatment methods consisted of further local excision with or without colostomy or abdominoperineal resection. Patients with coexisting visceral adenocarcinomas were all treated by abdominoperineal resection and the one with an adenocarcinoma of the colon was treated by a left-sided hemicolectomy.

Crude survival rates

Nine patients died during the observation period from their malignancy. Thirteen patients were alive, two with non-*in situ* Paget's disease of the anal margin and 11 without Paget's disease of the anal margin.

Figure 3 shows the survival rates estimated by life-table analysis for patients with Paget's disease of the anal margin and a normal Danish population of equal age and sex distribution. The 5-year survival rate was almost 54 per cent compared with 84 per cent for the normal population ($P<0{\cdot}01$). The corresponding values at 10 years were 45 per cent and 60 per cent ($P<0{\cdot}01$).

Discussion

It seems obvious from the present study that Paget's disease of the anal margin appears in three forms: an invasive, an *in situ*, and a non-invasive non-*in situ* form. However, it is not clear whether these represent different diseases or whether they are the same disease in different stages of development[2]. The last possibility seems most likely, since we have found that the *in situ* form re-occurs in the invasive form several years after apparently radical treatment.

The study emphasizes the importance of long follow-up of radically treated patients with Paget's disease of the anal margin. Sixty-one per cent of the patients developed recurrent disease up to 8 years after primary radical treatment.

As pruritus ani, which was by far the commonest presenting symptom, is such an obvious symptom, it might be expected that a physician would be consulted soon after the onset of the symptoms and that biopsy would be performed promptly. However, it must be emphasized that all patients had an

Table 2 *Recurrent Paget's disease of the anal margin (PAM) and its secondary treatment*

Recurrent lesion (*n*)	Secondary treatment (*n*)	Follow-up status
PAM (5)	Local excision with temporary colostomy (2)	Both alive 2 and 5 years later without PAM
	Local excision (3)	All alive 3–4 years later without PAM
Invasive PAM (4)	Abdominoperineal resection (3)	All died from metastases within 9 months
	Local excision (1)	Alive 9 years later without PAM
PAM plus coexisting visceral carcinoma (2)	Abdominoperineal resection (2)	One died 6 months later from metastases One alive 18 months later without PAM or visceral carcinoma

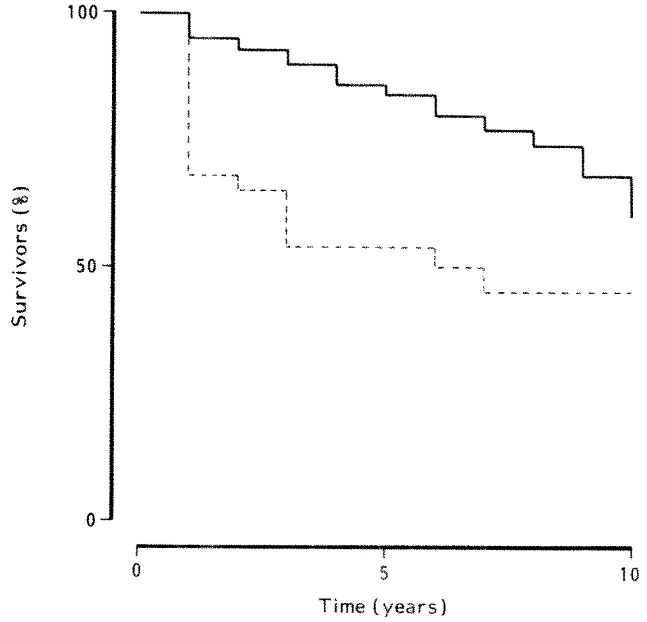

Figure 3 *Crude survival rates (life-table analysis) for patients with Paget's disease of the anal margin (– – –) and for a normal population of the same age and sex distribution (——)*

erroneous diagnosis made at first physician visit (like most other patients with malignancies of the anal region), and were treated by various ineffective creams for a considerable period of time before biopsy was undertaken[8]. This mistake may have been fatal for the patients with invasive Paget's disease of the anal margin. Thus, in order to improve the prognosis for these patients and to obtain a diagnosis in patients with persistent pruritus ani, it should be emphasized that these patients should be biopsied more frequently than has been the case hitherto.

Extended surgical excision seems to be the treatment of choice for patients with non-invasive Paget's disease of the anal margin and without coexisting visceral malignancy. The disease tends to recur following small local excisions. Curettage and radiotherapy were followed by recurrent disease in all cases, but the number of patients treated was too small to allow any conclusion about the efficacy of curettage and radiotherapy in the treatment of Paget's disease of the anal margin. In contrast, non-invasive recurrent Paget's disease of the anal margin is cured by extensive local excision with or without colostomy for at least the length of the observation time reported here. In general, the more radical the surgical excision, the more favourable the prognosis.

If histopathological examination reveals invasive Paget's disease of the anal margin the prognosis is poor, despite abdominoperineal resection, since most patients already have distant metastases at the time of diagnosis. However, one of our patients with invasive Paget's disease of the anal margin without distant metastases appears to have been cured by an extended local excision and a temporary colostomy.

Since the risk of having or developing a cancer is substantial among patients with Paget's disease of the anal margin, effective cancer prophylaxis implies control examinations at suitable intervals even after apparently radical treatment. The duration of this control period is not clear. According to the present study a follow-up period of 5 years seems to be insufficient, since recurrences occurred up to 8 years after treatment. Therefore, we consider that life-long surveillance is well founded at least until results from larger series contradict this approach. The control examinations should at least include a physical examination, proctosigmoidoscopy, double contrast barium enema, and biopsy of the perianal region once a year.

Our incidence of invasive Paget's disease of the anal margin with or without a coexisting visceral malignancy seems lower than that previously reported[11]. The reasons for this discrepancy could be that most previously reported cases are from small series treated in a hospital, whereas most of our cases with small non-invasive lesions were treated in the physician's office. It seems likely that patients with invasive lesions or coexisting visceral carcinomas are referred to treatment in hospitals, whereas small non-invasive lesions are treated in outpatient clinics or in the office of a practising dermatologist or surgeon. Therefore, series reported from hospitals alone might give a false impression of the incidence and natural history of Paget's disease of the anal margin.

Acknowledgements

We wish to thank our colleagues for the submission of tissue specimens.

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A new non-operative approach to fistula in ano

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The results of a new out-patient approach to fistula in ano *are presented. The technique involved passing a multi-strand stainless steel wire through the fistulous tract and has been used in 56 patients with low fistulae as well as high horseshoe anal fistulae. Recurrence was seen in only 2 patients and none of the patients experienced temporary or permanent incontinence of flatus or faeces.*

Keywords: Fistula *in ano*, wiring

Fistula *in ano* is a common surgical problem. The usual treatment is surgical excision with healing by open granulation. This orthodox procedure requires hospitalization and is associated with wound and sphincter problems in high anal fistulae. The present report describes insertion of braided stainless steel wire as the primary out-patient treatment (without any operation) for all types of fistulae *in ano*.

Patients and methods

This study was undertaken in a single surgical unit of the Department of Surgery, All India Institute of Medical Sciences, New Delhi between November 1984 and December 1986. All patients who presented with perianal discharge with a visible external opening in the perineum were prospectively included in the study. A detailed history was taken and a thorough clinical examination was performed to rule out the possibility of any underlying problem leading to the fistula *in ano*. If there was any suspicion of associated disease as a cause of fistula *in ano*, further investigations were done and all the secondary fistulae were excluded.

Technique

The wire was inserted when there was no discharge of pus or minimal discharge without any perianal inflammation. Patients who had significant pus discharge were treated with appropriate antibiotics and sitz baths before the procedure. The technique was undertaken in a minor operation theatre of the surgical out-patient department under regional anaesthetic or caudal block and with the patient placed in the lithotomy position. The fistulous tract was gently probed with a malleable probe with an eye, the probe being inserted through the external opening. The internal opening was negotiated by gradually manoeuvring the tip of the probe against the wall of the anal canal. In a situation where the internal opening could not be negotiated with ease, the probe was pointed at the highest point of the track and an internal opening was created at the suspected weak point in the wall of the anal canal. The probe was advanced to bring its tip out through the anus and a No. 1 braided stainless steel wire was threaded into the eye of the probe. The probe was then withdrawn through the anal canal leaving the wire lining the fistulous tract with one end projecting through the anus and the other through the external fistula opening. Both ends of the wire were secured separately with the two artery forceps to avoid the wire slipping (*Figure 1*). The two ends of the wire were then twisted in clockwise direction so that the 'knot' was snugly apposed to skin with a fairly tight grip around the fistulous tract and without any sign of looseness (*Figure 2*). The redundant wire was then cut off, leaving a small stump which could easily be caught and twisted subsequently.

After wiring, patients were given liberal analgesics; antibiotics were prescribed only when there was pus discharge. Patients were advised to have sitz baths twice a day and to maintain perianal hygiene. The patients were examined after 1 week, when the wire loop had become loose after cutting through part of fistulous tract. The wire was then twisted tighter in a clockwise direction until it became taut or the patient complained of pain. This procedure was repeated weekly until the wire had completely cut through the fistulous tract. The patients were called back after 4 weeks to ensure complete healing with subsequent follow-up every 3 months for 1 year and every 6 months for another 3 years.

Details of patients

The age of the patients ranged from 16 to 71 years and 33 of them were in the age group 21–40 years; the male:female ratio was 7:1.

There was history of drainage of perianal abscess in all the 56 patients and the duration of fistula *in ano* varied from 15 days to 20 years. No less than 26 patients had a fistula duration of more than one year. Recurrent fistulae *in ano* were present in seven (13 per cent) patients. In two patients there was history of pulmonary tuberculosis which was adequately treated; both patients had recurrent fistulae.

The distance of the external opening from the anal verge varied from 0·5 cm to 10 cm. There were 59 external openings in 56 patients, 3 patients having two openings. Eleven patients had an external opening within 2 cm of the anal verge lying posteriorly between the 3 o'clock to 9 o'clock position, while all of the 15 openings at a distance of more than 3 cm were placed posteriorly. In all, 26 external openings were anteriorly placed, while 33 opened posteriorly. In the three patients with two external openings, both were placed posteriorly. It was possible to negotiate the internal opening in 53 of the 59 fistulae (90 per cent) (that is 50 patients) while in 6 cases an internal opening was created at a highest weak point of the anal canal.

The 59 anal fistulae were classified according to Parks *et al.*[1] as follows: 38 (64 per cent) intersphincteric; 9 (15 per cent) low trans-sphincteric; 6 (10 per cent) high trans-sphincteric; and 2 (3 per cent) suprasphincteric. In addition there were four patients with a subcutaneous tract (subsphincteric). Horseshoe fistulae with two external openings were present in three patients. Wiring of both the horseshoe tracts was performed simultaneously.

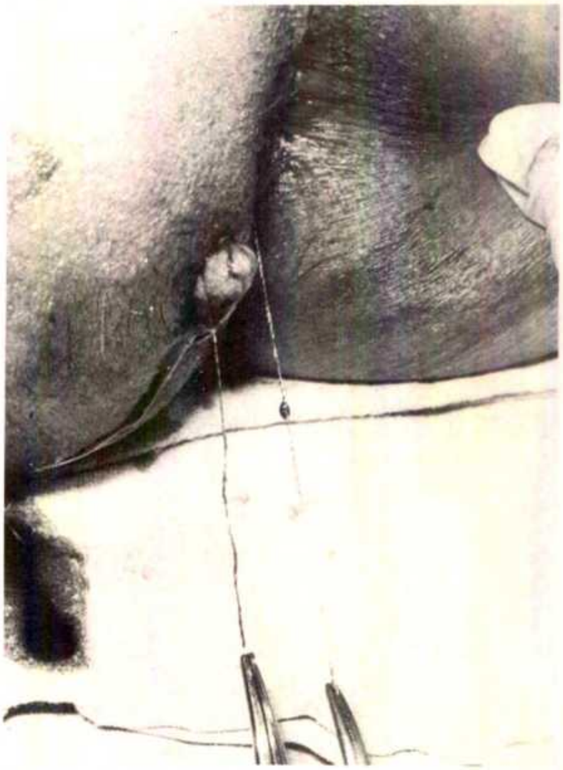

Figure 1 *A probe, with wire threaded into its eye, is passed along the course of the fistulous track*

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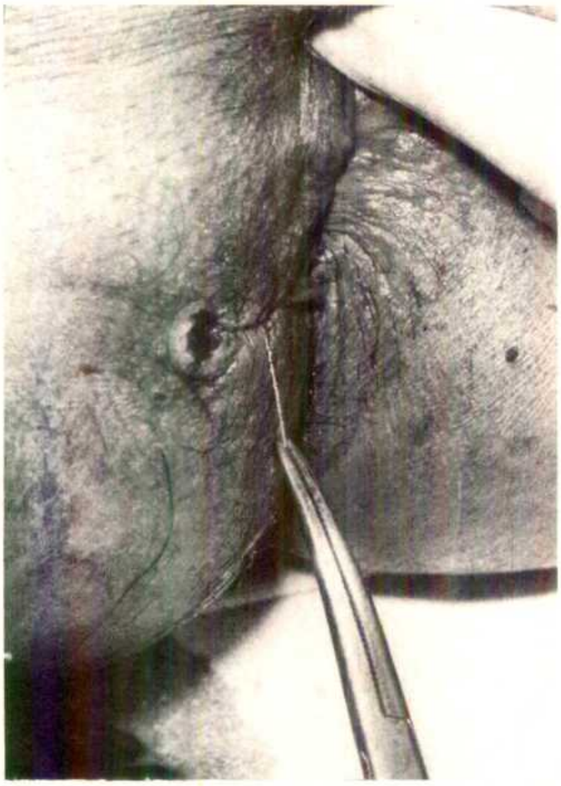

Figure 2 *The wire is twisted clockwise and then the redundant portion is ready to be cut*

Results

The time taken for complete healing varied from 4 days to 7 weeks (average 3·6 weeks). It took less than 7 days in subcutaneous tract fistulae, and 3, 4 and 5 weeks respectively for low anal canal fistulae with external openings at a distance of 1–1·5, 2–2·5 and 3–3·5 cm from the anal verge. It took more than 5 weeks (5 patients) and 7 weeks (3 patients) for healing if the external fistulous opening was at 5 cm or more from the verge. The number of 'tightenings' required for the wire to cut out and achieve complete healing ranged from 1 to 8 sittings with an average of 4·5.

Complications and final result

Complete follow-up data were available in 53 patients (56 fistulae). All patients experienced pain for the first 2 days after wiring. Six patients continued to have significant pus discharge requiring antibiotics, minor bleeding was noticed in 3, and perianal cellulitis occurred in one patient, who required intensive antibiotics for 1 week. None of the patients complained of temporary or permanent incontinence of flatus or faeces during the period the wire was *in situ*.

The duration of follow-up in the 53 reviewed patients varied from 11 to 37 months (average 22 months). Recurrence of fistula *in ano* was seen in two patients; both recurrences developed within 6 months and both were treated successfully by rewiring. None of the patients complained of temporary or permanent anal incontinence of either flatus or faeces, after the procedure.

All of the reviewed patients were quite satisfied with their treatment at the time of the closure of the fistula although three patients commented that they would have preferred local anaesthesia to avoid pain at the time of tightening of the wire.

Discussion

The conventional operative treatment of low fistula *in ano* is to lay open or completely excise the fistulous track and allow healing by open granulation. In high anal fistulae, complete excision is not possible and the operative procedure has had to be modified to consist of partial excision along with the use of a seton to achieve cure[2–4]. These operative procedures leave an open wound which requires 4–5 weeks to heal for a low anal fistula and 12–16 weeks for a high horseshoe fistula. Operative procedures such as laying open the fistula with immediate skin grafting and secondary or delayed skin grafting are cumbersome and involve a great deal of theatre time, while fistula excision with primary suture carries a recurrence rate of approximately 50 per cent with the added morbidity of sepsis of the perianal wound[3]. In addition, these operative treatments of fistulae *in ano* involve prolonged convalescence in hospital and frequent painful dressings of the perianal wound. Furthermore these procedures are not suitable for high anal fistulae as there is always the risk of permanent anal sphincter damage particularly in inexperienced hands. The results of the various operative procedures in a relatively large series of 199 patients followed on average for 9 years have recently been reported[5]. In this study, recurrence was seen in 11 per cent of patients, while 34 per cent experienced temporary mild defects in anal control. Ramanujam *et al.*[6] found temporary incontinence for flatus in all of their patients while in 2·2 per cent of cases this problem proved permanent; they also reported a 2·2 per cent recurrence rate. In the present study, treatment of the fistulae *in ano* by wiring was attended by a recurrence rate of 4 per cent (2 fistulae) within 6 months. More importantly, none of the patients so treated complained of temporary or permanent incontinence for flatus or faeces. In both patients with recurrence, rewiring proved successful.

The advantages of wiring are that it is an out-patient procedure which can be done under caudal block or regional anaesthesia in a minor operation theatre. The procedure does not require hospitalization and decreases considerably the load on in-patient services.

Patients can return to work on the same day and are not left with a large perianal wound and its associated morbidity.

Acknowledgements

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Increase in pudendal nerve terminal motor latency with defaecation straining

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The relationship between perineal descent and pudendal nerve damage was tested in 57 consecutive patients by measuring the left and right pudendal nerve terminal motor latency (PNTML) before and after a maximal defaecation straining effort. In 13 patients the PNTML was also measured 1 and 4 min later. The difference between the mean PNTML before and after straining (ΔPNTML) was correlated with the amount of descent ($r=0{\cdot}40$, $P<0{\cdot}005$), *and with the perineal position during straining* ($r=-0{\cdot}46$, $P<0{\cdot}001$). *Four minutes after the straining effort the PNTML again approached the resting value in each subject. These findings support the concept that perineal descent causes pudendal nerve damage.*

Keywords: Anal sphincter, electromyography, nerve conduction

There is evidence that denervation of the external anal sphincter and pelvic floor muscles may occur after vaginal delivery[1] and also in association with a history of excessive straining on defaecation[2]. Pudendal nerve damage can be assessed by measurement of the pudendal nerve terminal motor latency (PNTML)[3]. Abnormal descent of the pelvic floor occurs in many patients with pudendal neuropathy[4–6] which is itself found in idiopathic faecal incontinence and urinary stress incontinence[4,6–11]. The relationship between perineal descent and prolonged PNTML has been evaluated statistically in patients with constipation[2] and faecal incontinence[3,6] and following vaginal delivery[1]. However, it is not possible from these studies to determine whether abnormal perineal descent directly results in pudendal nerve damage. Therefore, we have looked for direct evidence that perineal descent results in damage to the pudendal nerves, and have examined the relationship between nerve damage and the degree of perineal descent.

Patients and methods

Fifty-seven consecutive patients were studied. There were 15 men and 42 women, mean age 52 years (range 26–80 years) Twenty-six had idiopathic (neurogenic) faecal incontinence and 12 had severe constipation The remaining diagnoses included idiopathic perineal pain (8), external anal sphincter injury (4), anterior mucosal prolapse (4) and solitary rectal ulcer syndrome (3). Of the 57 patients 28 had faecal incontinence.

Perineal descent

The position of the perineum at rest and during a defaecation straining effort was measured with respect to the plane of the ischial tuberosities using the St. Mark's perineometer as previously described[12] In normal subjects the perineum is 2·5 ± 0·6 cm (s.d.) above the plane of the ischial tuberosities at rest, and 0·9 ± 1·0 cm above this plane during straining[12]. The perineal position was considered to be abnormal if it lay below the level of the ischial tuberosities during defaecation straining.

Pudendal nerve terminal motor latency

The PNTML was measured by transrectal stimulation of the pudendal nerves[3]. Square wave supramaximal stimuli were delivered to the left and right pudendal nerves and the compound muscle action potentials were recorded in the external anal sphincter The patient was then asked to carry out a maximal defaecation straining effort sustained for as long as possible, usually for about 60 s. Care was taken to ensure that the patient did not contract the external anal sphincter and pelvic floor muscles, and thereby produce a Valsalva manoeuvre, by observing a relaxation of the anal sphincter ring and descent of the pelvic floor. This ensured that a true defaecation strain with maximal pelvic floor descent occurred in each case. During the straining effort the examining finger with pudendal nerve stimulator was left in the anorectum. This prevented the passage of flatus or stool and assisted in encouraging a maximal straining effort by allaying fears of patient embarrassment The left and right pudendal latencies were measured immediately after the end of the straining effort. In 13 patients the latencies were again recorded 1 and 4 min later. Each recording was made with the observer unable to visualize the digital print-out of the latency, in order to eliminate bias based on knowledge of the amount of perineal descent The mean value of the left and right latencies for any given recording was calculated and termed the mean PNTML In our laboratory the mean PNTML at rest is 2·0 ± 0·2 ms (s.d.)[3,13].

Statistical analysis

The data were compared using the two-sample test. Changes in PNTML were correlated with perineal descent using linear regression analysis.

Results

The PNTML was increased on straining in 28 patients, decreased in 5 patients and in 24 it remained constant (*Figure 1a*). Twenty-six patients had abnormal perineal descent on straining (Group 1) and in 31 there was no abnormal descent (Group 2). There was a significant difference in PNTML between these two groups at rest ($P<0{\cdot}001$) and immediately after straining ($P<0{\cdot}001$). There was a significant increase in PNTML after straining in Group 1 patients with abnormal perineal descent ($P<0{\cdot}05$) but not in Group 2 ($P=0{\cdot}45$). Eighteen patients (69 per cent) in Group 1 and ten (32 per cent) in Group 2 showed an increase in PNTML on straining.

There was a significant correlation between the difference in mean PNTML before and after straining (ΔPNTML) and the amount of perineal descent ($r=0{\cdot}40$, $P<0{\cdot}005$) (*Figure 1a*), and between ΔPNTML and the position of the perineum relative to the transischial line on straining ($r=0{\cdot}46$, $P<0{\cdot}001$) (*Figure 1b*) This correlation also applied with independent assessment of left and right pudendal latencies (amount of descent: $r=0{\cdot}36$, $P<0{\cdot}001$; strain position: $r=-0{\cdot}39$, $P<0{\cdot}001$). The five patients in whom the PNTML was slightly decreased after straining are plotted as zero change in PNTML in *Figures 1a* and *1b* but the negative values were included in the correlations.

There was also a significant correlation between the latency coefficient expressed by

$$\frac{\text{PNTML}+\Delta\text{PNTML}}{\text{PNTML}}$$

and the amount of perineal descent ($r=0{\cdot}36$, $P<0{\cdot}01$). Significant correlations between ΔPNTML and the amount of perineal descent were seen both in incontinent ($n=28$, $r=0{\cdot}44$,

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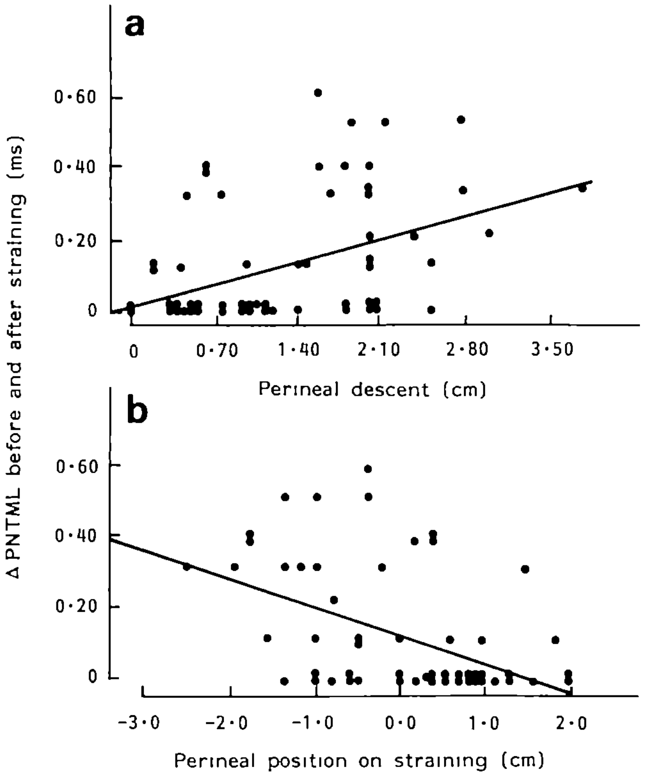

Figure 1 **a** *Regression analysis showing relationship between amount of perineal descent and change in pudendal nerve terminal motor latency* (*ΔPNTML*) *with defaecation straining* ($r=0{\cdot}40$, $P<0{\cdot}005$). **b** *Regression analysis showing relationship between the perineal plane on defaecation straining and change in PNTML with straining* ($r=-0{\cdot}46$, $P<0{\cdot}001$). *The position of the perineum above the plane of the ischial tuberosities is shown as a positive value and below this plane as a negative value. There was abnormal perineal descent in 26 patients*

$P<0{\cdot}025$) and in continent subjects ($n=29$, $r=0{\cdot}39$, $P<0{\cdot}05$). In addition significant correlations between ΔPNTML and the perineal position during straining were also found in incontinent ($r=-0{\cdot}45$, $P<0{\cdot}025$) and continent ($r=-0{\cdot}43$, $P<0{\cdot}025$) subjects.

In the 13 subjects tested 1 and 4 min after straining, the PNTML increased on straining in nine and in each case approached the resting value at 4 min (*Figure 2*).

On straining the PNTML increased from a normal to an abnormal value ($>2{\cdot}4$ ms) in eight subjects, six of whom had abnormal perineal descent. The amount of perineal descent ($P<0{\cdot}05$) and the position of the perineum during straining ($P<0{\cdot}01$) were significantly different in this group of eight subjects compared with the values in the 42 subjects in whom PNTML remained within normal limits after straining. However, there was no significant difference in the amount of perineal descent or strain position between these eight patients and seven in whom the PNTML was abnormal at rest.

Discussion

Increase in the latency of motor conduction in the pudendal nerve (PNTML) is a direct measure of nerve damage[3]. We have previously shown a significant correlation in the PNTML both with the amount of perineal descent and the position of the perineum on straining in patients with idiopathic faecal incontinence[6] Parks *et al.*[14] originally suggested that straining at stool could cause abnormal perineal descent. They observed that weakness of the pelvic floor musculature and anal sphincter, and faecal incontinence were found in some patients with perineal descent. With the demonstration that idiopathic faecal incontinence was associated with neuropathic changes in the external anal sphincter and puborectalis muscles, it then was proposed that straining leading to perineal descent might damage the nerves supplying the pelvic floor[3,4,12]. The results of the present study give evidence that this sequence of events can occur. Straining in our patients produced a significant functional deterioration in pudendal nerve conduction. This association between perineal descent, pudendal nerve damage and sphincter denervation is supported by histological[7] and electrophysiological[4,5,8,10,11,13] evidence of re-innervation in the external anal sphincter and puborectalis muscles, and slowing of conduction in the pudendal nerves[3,6], in patients with perineal descent and faecal incontinence.

Chronic straining at stool is not the only factor causing pudendal neuropathy; damage to the pudendal nerves and to the pelvic innervation of the puborectalis muscle occurs during vaginal delivery[1]. Risk factors for this nerve damage include prolonged second stage of labour, forceps delivery, third degree perineal tear and high infant birth weight[1]. During vaginal delivery a number of factors may be responsible for nerve damage, including plevic floor descent and direct injury to the pudendal and other pelvic nerves by the passage of the fetal head through the pelvis. Nerve damage results in denervation and weakness of the muscles of the pelvic floor, and in perineal descent, which itself may result in abnormal stretching of the terminal portion of the pudendal nerves, with consequent stretch-induced injury.

Thus perineal descent and pelvic nerve damage are related findings[3–6,10,11,13] and it would appear that each may lead to the other. The evidence for this vicious circle has hitherto been circumstantial. Our results show that perineal descent produced by a simulated defaecation straining effort caused a transient increase in the PNTML in some patients. This observation has

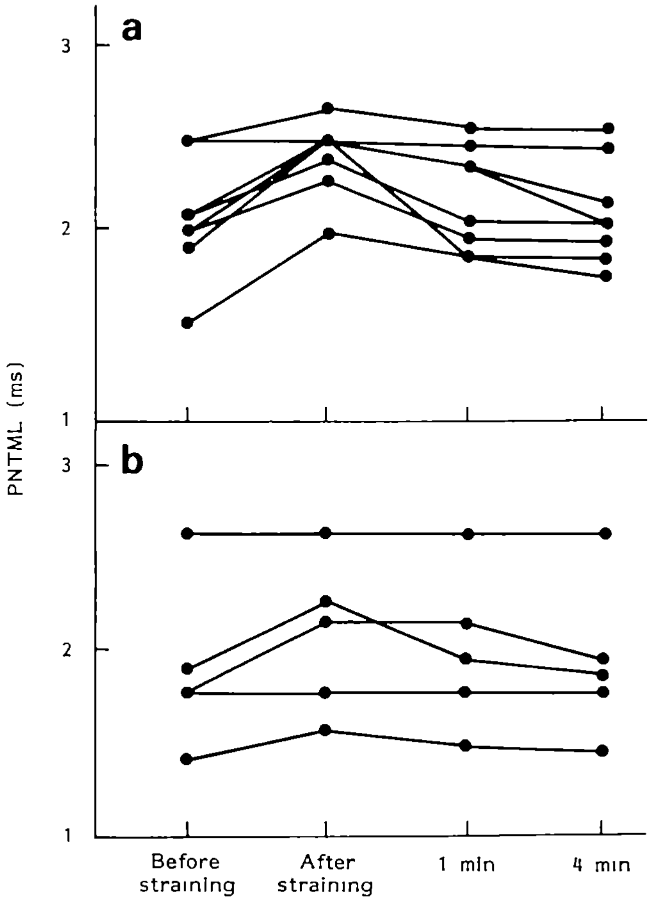

Figure 2 *Change in PNTML before and after straining, and 1 and 4 min after cessation of straining, in the 13 patients in whom all four recordings were made.* **a** *Patients with abnormal perineal descent,* **b** *patients without abnormal descent. The straining effort increased the PNTML from normal into the abnormal range in 4/8 subjects with abnormal perineal descent, three had neurogenic incontinence and one had anterior mucosal prolapse*

only been made in patients with pelvic floor disease as the study did not include a population of normal patients. However the significant correlation between the increase in PNTML and the extent of perineal descent implies that normal subjects without abnormal perineal descent would have a small increase or no increase in PNTML on straining.

The PNTML is measured by delivering five or more supramaximal electrical stimuli to the pudendal nerve at 1 s intervals and storing the sequence of tracings on the oscilloscope screen for measurement of latency between stimulus and muscle response[2,3]. The PNTML was slightly decreased after straining in five of the 57 patients. Reproducibility of measurement of PNTML was not specifically tested in this study but the technique used minimized possible variation in the latency due to a change in the position of the stimulating electrode. Our normal data for PNTML have been tested by different investigators in our laboratory since this test was developed in 1983 and these data are consistent[1–3,6].

Whilst the increase in PNTML with straining may not necessarily be the basis for the permanent nerve damage seen in these patients, there is evidence from studies of other peripheral nerves that transient slowing of conduction follows a stretch-induced neurapraxia[15,16]. Tests measuring latency of conduction have been applied to patients with the carpal tunnel syndrome to demonstrate the effect of compression of the median nerve on wrist flexion[17]. The present observation provides direct support for the hypothesis that recurrent stretch-induced injury due to abnormal perineal descent results eventually in permanent pelvic and pudendal nerve damage causing weakness of the striated pelvic floor sphincter muscles sufficient to lead to faecal and stress urinary incontinence.

It is difficult to devise a protocol for a standardized straining effort. This would require each patient to strain for the same amount of time and with the same effort. The latter is difficult to control except over a very short time-span. In addition, for all patients to comply, it would be necessary to use as the standard a short straining time with a small exertional effort. We have therefore relied on the patient making a maximal straining effort rather than attempting to establish a standard strain for a standard period of time.

Not all the patients with abnormal perineal descent showed an increase in PNTML on straining, and nearly a quarter of those without abnormal descent showed a small increase. None the less, overall there was a significant correlation between these two variables. The observation that this correlation was found both in continent and incontinent subjects and that the PNTML increased in proportion to the pre-straining latency supports our theory that the denervation process is progressive. Measurement of PNTML before and after straining may provide additional information of clinical relevance in the investigation of patients with incontinence. In those with abnormal perineal descent and a pudendal nerve latency in the upper part of the normal range at rest, evidence of neuropathy may be apparent only when PNTML is measured after straining.

Acknowledgements

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Use of staplers on oesophagogastric varices

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Thirty-five gastrofundic devascularization procedures were performed with the side-to-side CF stapler of Chinese manufacture for obliteration of oesophagogastric varices. Four patients were operated on as emergencies, six patients 2–3 weeks after control of bleeding by tamponade and the remaining twenty-five electively (including four patients who had not bled). There were two operative deaths, an operative mortality of 6 per cent. In all, 30 patients have been followed, 20 for 1–3 years and 10 for less than 1 year. Twenty-five patients had postoperative barium meal examination. The varices were ameliorated in 19, not changed in 5 and exacerbated in 1. Nine patients rebled and of these, two died. The stapler is used in devascularization to interrupt intramural varices in the oesophagocardiac region. It must be emphasized that its use is only a part of the devascularization procedure. When used alone devascularization is not complete. The side-to-side stapler appears to be a convenient, safe and rational instrument for use in devascularization.

Keywords: Portal hypertension, oesophageal and gastric varices, surgical staplers

Porta-systemic shunts have been employed to treat oesophagogastric varices since the 1940s. The procedure decreases the rebleeding rate, but diverts blood flow away from the liver and may lead to hepatic encephalopathy and progression of hepatic insufficiency. Consequently, devascularization operations have been used by some surgeons in an attempt to eradicate varices without damaging effects on liver function.

Recently, an intramural network of varices between the inner circular and outer longitudinal muscle layers has been recognized in patients with portal hypertension. It connects the peri-oesophageal varices with submucosal varices in the oesophagocardiac region[1]. Any devascularization procedure for the treatment of oesophageal variceal bleeding must interrupt this variceal network. This has meant transection and reanastomosis of the oesophagus using a tubular stapler, and the procedure can be performed with relative ease and safety. In 1975 Rinecker and Danek[2] reported on the use of a linear stapler to interrupt gastrofundic varices. In 1979 we pioneered in China the use of a tubular stapler in cardiectomy with oesophagogastrostomy[3,4]. In 1983 we also began to perform gastrofundic devascularization using the side-to-side† CF* stapler[5]. Here we report our preliminary experience with the CF stapler in this context.

Patients and methods

Thirty-five patients (28 men and 7 women, age 20–63 years) have been subjected to gastrofundic devascularization with the side-to-side CF stapler between January 1983 and February 1987 The cause of the portal hypertension was hepatitis (21 cases), schistosomiasis (7 cases), mixed causes (6 cases) and congenital extrahepatic cavernous transformation of the portal vein (1 case) By Child's classification[6], 7 patients were in grade A, 18 in grade B and 10 grade C. Sixteen patients (46 per cent) had had up to three previous operations. The operations were. splenectomy (13 cases), splenorenal shunt (3 cases); mesocaval H shunt (2 cases) and transgastric varix ligation (3 cases). Pre-operative barium meal examination was performed in 34 patients· all had varices and 22 of them were judged to be severe. Four patients who failed to respond to non-surgical treatment were operated on as emergencies. Six patients were operated on 2–3 weeks after control of massive haematemesis by balloon tamponade. Twenty-five patients were operated on electively and, of these, four were prophylactic operations in patients who had not bled.

At operation the right gastro-epiploic vein was catheterized for portal pressure measurements. Readings were also taken after removing the spleen, after devascularization of the distal oesophagus and cardia, and after gastrofundic devascularization with the linear stapler Pressure readings were subjected to the Dunnett's *t* test to assess the significance of observed differences The survival and freedom from rebleeding rates were assessed using the Kaplan–Meier method.

Operative procedure

The operation is usually carried out transabdominally but in five patients undergoing reoperation we elected to use a transthoracic approach The first step is splenectomy. The second step is extensive devascularization which involves the upper half of the stomach and distal oesophagus for at least 5 cm The third step is a gastrofundic devascularization performed with the side-to-side CF stapler. A stab wound is made on the lesser curvature about 3 cm below the oesophagogastric junction. One (anvil) fork of the stapler is inserted obliquely into the gastric lumen directed towards a point about 3 cm below the oesophagogastric junction The cartridge fork is placed on the anterior serosal surface. The stapler is closed Because the stapler is used for devascularization, the push bar has no median knife· After firing, four parallel rows of staples transfix the varices anteriorly The stapler is re-applied posteriorly The stab wound is closed with sutures after retrieving the stapler. If the operation is being conducted through a transthoracic approach, then the stab wound is made on the greater curvature

Results

The results of intra-operative portal pressure measurement show that mean portal pressure rose from $36{\cdot}7 \pm 8{\cdot}7$ mmHg before gastrofundic devascularization to $38{\cdot}7 \pm 9{\cdot}1$ mmHg thereafter ($P < 0{\cdot}05$). Two patients died in hepatic coma as a result of rebleeding on the fifth and sixth postoperative day respectively to give an operative mortality of 6 per cent. Two patients developed a subphrenic abscess but recovered after drainage.

Three patients were lost to follow-up. In all, 30 patients could be traced, 20 for 1–3 years and 10 for less than 1 year. During follow-up, two of these patients died because of massive haematemesis at 6 and 8 months respectively after operation The postoperative survival rate is shown in *Figure 1* A postoperative barium meal examination in 25 patients showed

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* CF is the abbreviation of the Chinese name of the side-to-side stapler.

† Designed and manufactured by Zhong Shan Hospital and Shanghai 6th Surgical Instrument Factory

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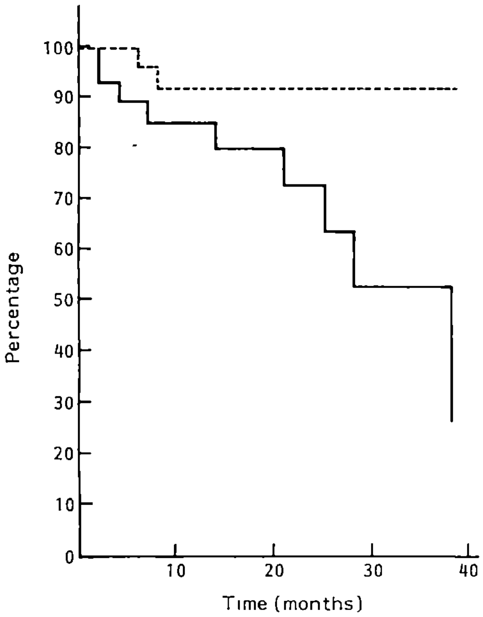

Figure 1 *Survival and freedom from rebleeding following stapler devascularization* ——, *survival rate,* ——, *proportion of patients remaining free from rebleeding*

disappearance of varices in 3, improvement in 16, no change in 5 and exacerbation in 1 (an improvement rate of 76 per cent). In the follow-up period, 9 patients rebled while 19 did not, a further 2 non-bleeders having had prophylactic operations. The proportion of patients free from rebleeding is also shown in *Figure 1*. Four of the nine patients with rebleeding had massive haematemesis as defined by a systolic blood pressure of <90 mmHg and a heart rate >120 beats per minute, while the other five had mild haematemesis and melaena. Of the latter five cases, all but one patient did not need balloon tamponade and bleeding stopped spontaneously. In one of these patients who had massive haematemesis at 7 months, after control of bleeding by balloon tamponade, barium meal examination showed that varices were still present. Percutaneous portal venography was then performed. There were varicose portal and superior mesenteric veins, but portoazygos collaterals in the oesophagocardiac region were not seen.

Discussion

Oesophageal and gastric varices may coexist in portal hypertension. Before oesophageal transection is performed, the gastric fundus must be explored. If gastric fundal varices are present, they must be ligated, irrespective of whether they are ruptured, so as to reduce the chance of their bleeding postoperatively. When transection is performed, the level normally recommended is about 2 cm above the cardia[7] However, venous stasis makes the oesophageal wall friable, and it may be inadvertently damaged during oesophageal dissection. Furthermore, as there is no serosa and the blood supply comes only from the descending aorta, healing may be compromised after the distal oesophagus has been dissected extensively and transected. Therefore, we strongly recommend gastrofundic devascularization below the level of the cardia, using the side-to-side stapler[5]. This has four advantages: there is neither tension nor stricture at the interruption site, gastric and oesophageal varices are disconnected simultaneously without transecting the fundus; distal oesophageal function is normal, and the presence of the serosa and good blood supply aids healing.

The main collaterals in the oesophagocardiac region are the oesophageal, gastric and high oesophageal branches of the coronary vein[8]. The secondary collaterals are the short gastric, left inferior phrenic and posterior gastric veins as well as intramural varices in the oesophagocardiac region. It must be emphasized that application of the stapler interrupts the intramural varices only. Complete devascularization must include interruption of all of the above collaterals. It is essential to obtain optimal exposure, and a transthoracic approach may be preferred, as in five of our patients undergoing reoperation.

During the operation we consider that the vagus nerves should be protected if possible. Although highly selective vagotomy can be performed simultaneously[7], it is a very difficult undertaking, especially in patients undergoing emergency devascularization. However, the major objectives are to keep operating time short and avoid injury to the oesophageal wall. Barium meal examination in 11 of our patients with known injury to the vagus nerves suggests that postoperative gastric stasis is not a problem. Gastric emptying was normal in seven of these patients and the remaining four patients had only slight delay in gastric emptying. None of them experienced significant postprandial epigastric fullness or distension. Therefore, dissection of the vagus nerves should not be overemphasized in case of accidental vagus nerve injury, routine pyloroplasty is probably unnecessary.

The methods available for the assessment of oesophageal varices include barium swallow, endoscopy and angiography although no method is infallible. Fibreoptic endoscopy is not always acceptable to the non-bleeding patient, while angiography is an invasive procedure and is not always available. Barium meal examination has its inherent faults but may be less objectionable to the patients and Postlethwait[9] considered it to be of value in a patient who is not bleeding. Consequently, we relied on this method for follow-up. In the 25 patients who had had postoperative barium meal examinations, 76 per cent showed improvement, including complete disappearance of varices in 3.

The results of our intra-operative portal pressure measurements show that interruption of retrograde flow in the intramural varices is necessary, because average portal pressure was increased after fundic devascularization. This increased pressure may be helpful in portal perfusion of the liver once varices have been eradicated. In our patient with rebleeding in whom the thoroughness of devascularization was confirmed with angiographic studies, rebleeding must be attributed to local factors. It is possible that atrophic changes in the oesophagogastric mucosa secondary to hypoxia from chronic venous congestion predisposed the varices to rupture in this patient[10].

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Adjuvant treatments following curative resection for gastric cancer

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The results of a prospective randomized trial of adjuvant treatment after curative resection for gastric cancer are reported. The study consisted of three arms: (1) surgery only; (2) chemotherapy (5-fluorouracil (FU) and 1-(2-chloroethyl)-3-(4-methylcyclohexil)-1-nitrosourea (Me-CCNU)) after surgery; (3) chemo-immunotherapy (FU, Me-CCNU and levamisole) after surgery. Between March 1977 and June 1981, 235 patients were included in the study by 18 co-operating institutions. Thirteen per cent of patients in arm 2 and thirteen per cent in arm 3 suffered major toxicity, necessitating interruption of treatment. Two of these patients died of marrow aplasia. Statistical analysis of survival showed that prognosis was influenced by the well-known prognostic variables, invasion of the wall, nodal status and site of tumour. The different treatments in the three arms, however, did not show any impact on prognosis, even when adjustments were made for the most relevant prognostic variables. Given the lack of effect on survival and the presence of clinically important toxicity, FU and Me-CCNU ± levamisole cannot be recommended as adjuvant therapy for resected gastric cancer.

Keywords: Gastric cancer, adjuvant treatment, randomized study

Although decreasing in overall incidence, gastric carcinoma is the second ranking cause of cancer mortality in Italy. In 1980, the age-adjusted mortality rate was 29·7 per 100 000 males and 18·2 per 100 000 females, thus representing 12·4 per cent and 11·7 per cent of the overall tumour mortality respectively[1,2].

In the 1960s, the Veterans Administration Surgical Oncology Group (VASOG) activated two randomized controlled clinical trials to evaluate the effect of single agent adjuvant chemotherapy in patients undergoing operation for carcinoma of the stomach. By 1974, several studies of adjuvant therapy after curative resection had been initiated, most of them in Japan. Results were at best inconclusive, some studies indicating no benefit for patients treated with adjuvant chemotherapy, while others, especially from Japan, suggested an improvement in survival[3].

The demonstration of activity of the nitrosoureas combined with fluorouracil in advanced gastric cancer was reported by the Eastern Cooperative Oncology Group (ECOG). Objective remissions were documented in 40 per cent of patients treated with semustine (1-(2-chloroethyl)-3-(4-methylcyclohexil)-1-nitrosourea or Me-CCNU) and 5-fluorouracil (FU) and were associated with a prolongation of median survival compared with Me-CCNU alone[4]. However, a subsequent study failed to confirm a survival advantage for patients treated with this combination compared with those treated with FU alone[5].

In 1971, Renoux and Renoux[6] first reported that levamisole, a pure chemical synthetic product, enhanced immune competence. The antitumour effect of this compound would be due to the fact that it activates and normalizes immune competence of the cancer-bearing body and enhances resistance to the tumour. This compound was then employed in a variety of non-gastrointestinal solid tumours, both as an adjuvant treatment and as a palliative treatment in advanced disease. However, long-term effects were questionable. In 1977, a prospective study was activated utilizing levamisole in patients with gastrointestinal cancers both as an adjuvant and as a palliative treatment (non-curative resection and inoperable disease) Miwa *et al.*[7] reported that levamisole prolonged survival in patients with gastrointestinal cancers, particularly when the tumour burden was decreased by surgery.

Thus, in 1977, the Italian Gastrointestinal Tumor Study Group activated a controlled randomized study aimed at assessing the therapeutic efficacy of chemotherapy (Me-CCNU plus FU) with or without levamisole in patients with gastric cancer following curative resection.

Patients and methods

Between March 1977 and June 1981, 18 institutions agreed to activate a prospective randomized study in patients with gastric cancer subjected to curative resection. Patients were allocated to receive either no further therapy after surgery, adjuvant combination chemotherapy, or adjuvant combination chemotherapy plus levamisole. Details of drug doses, sequences and treatment duration are reported in *Table 1*.

Eligibility criteria included: (a) complete removal of gastric cancer in patients not previously treated; (b) invasion of the gastric wall beyond the mucosa, (c) complete pathological evaluation to assess the histological type (according to Lauren classification), regional lymph node status and depth of wall invasion, (d) age ≤70 years; (e) absence of previous or concomitant malignancies (except for skin epithelial carcinomas); (f) absence of non-malignant systemic diseases preventing administration of the drugs under study, (g) recovery from acute effects of surgery and absence of infection within 45 days from operation; (h) patient consent and availability for frequent follow-up.

The surgical protocol required a curative resection, accepting the different procedures performed (total or subtotal gastrectomy and

Table 1 *Trial arms*

Randomization	
1	Surgery alone
2	Surgery + chemotherapy Me-CCNU 130 mg/m^2 p.o. day 1 FU 325 mg/m^2 i v. daily days 1–5 FU 375 mg/m^2 i v daily days 36–40 Repeat chemotherapy cycle every 10 weeks for 80 weeks
3	Surgery + chemo- and immunotherapy Me-CCNU and FU· the same as arm 2 Levamisole 150 mg daily days 11–13, 25–27, 46–48, 60–62 Repeat chemo-immunotherapy cycle every 10 weeks for 80 weeks

Me-CCNU, semustine or 1-(2-chloroethyl)-3-(4-methyl-cyclohexil)-1-nitrosourea; FU, 5-fluorouracil

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* *A list of participating members and institutions is given in the Appendix to this paper*

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Table 2 *Characteristics of the series in relation to treatment arms*

	Treatment arm			Total number of			
Variable	S	CT	CT + IT	patients	χ^2	d.f.	P
Sex							
Male	44	45	49	138	1·925	2	0·382
Female	25	30	20	75			
Age (years)							
31–60	42	46	40	128	0·250	2	0·882
>60	27	29	29	85			
Nodal status							
N−	33	30	26	89	1·611	2	0·447
N+	36	45	43	124			
Invasion of the wall							
pT1	17	11	12	40			
pT2	23	26	21	70	3·072	4	0·546
pT3–4	29	38	36	103			
Size of primary tumour							
<3 cm	25	12	19	56			
3–6 cm	24	34	24	82	9·179	4	0·057
>6 cm	11	21	14	46			
Undetected	9	8	12	29			
Histological type							
Intestinal	44	49	39	132			
Diffuse	20	21	25	66	1·444	4	0·836
Mixed	5	5	5	15			
Location of primary tumour							
Upper third	3	5	6	14			
Middle third	12	11	14	37	2·336	6	0·880
Lower third	43	45	38	126			
Other	11	14	11	36			
Surgical treatment							
Total gastrectomy	7	7	12	26			
Subtotal gastrectomy	55	50	49	154	7·225	4	0·124
Other	7	18	8	33			

S, surgery alone, CT, surgery + chemotherapy, CT + IT, surgery + chemo- and immunotherapy, N−, absence of involved regional nodes; N+, presence of involved regional nodes; pT1, invasion of the submucosa, pT2, invasion of the muscularis propria or the subserosa; pT3–4, invasion of the serosa or contiguous structures

various patterns of reconstruction), provided that they were adequately documented Careful inspection of the ovaries, peritoneum and liver was recommended Lymph node dissection of first level nodes and omentectomy were mandatory, whereas splenectomy and distal pancreatectomy were optional. Non-radical operation as assessed macroscopically or microscopically (tumour at the line of resection) as well as presence of distant metastases, even if resected, were reasons for disqualification. Histological type was categorized as intestinal, diffuse or mixed, and nodal status as either presence (N+) or absence (N−) of involved regional nodes. Invasion of the gastric wall was classified according to the 1978 TNM system[8].

Eligible patients were randomly allocated to one of the three treatments within 30 days from curative resection. During the first year, randomization, stratified by centre, was performed utilizing closed envelopes prepared by the data centre and distributed among participating institutions Since 1978, randomization took place centrally, via telephone calls to the data centre.

Adjuvant treatment was to be initiated within 45 days from surgical resection and a dose attenuation schedule for both Me-CCNU and FU was planned in the presence of haematological toxicity (white blood counts <4000/mm^3 and platelet counts <150 000/mm^3).

Complete physical examination as well as biochemical tests were planned every 10 weeks for the first 2 years and every 20 weeks thereafter. Radiological examinations and other non-invasive procedures were planned every 30 weeks. Criteria for recurrence included documentation by histological evidence or by radiological evidence for lung and bone metastases.

A total of 235 patients were entered into the study, but 22 were subsequently excluded because they did not fulfil eligibility criteria. Of the 213 evaluable patients, 69 were in arm 1 (surgery only; S), 75 in arm 2 (surgery plus chemotherapy; CT) and 69 in arm 3 (surgery plus chemo- and immunotherapy; CT + IT). Not all evaluable patients adhered to the planned follow-up timing and methods, mainly for psychological reasons, and this prevented adequate evaluation of disease-free survival. In patients not known to have died at the date of present analysis, median follow-up for the entire series was 81 months with some differences among the three treatment arms (80 months for S, 74 for CT and 81 for CT + IT, respectively).

Statistical analyses

All analyses were carried out according to the 'intention to treat' principle. The comparability of the three arms in terms of clinical and histological features of patients was assessed by the χ^2 test.

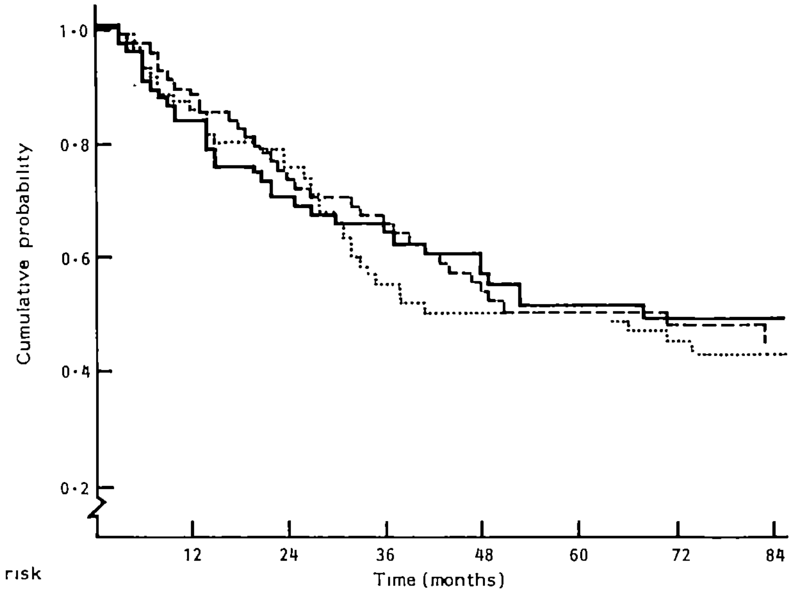
Death from all causes was taken as the endpoint and survival was measured from the date of surgery. The product limit method[9] was adopted to estimate survival curves in each arm. The null hypothesis concerning the differential effect of treatments was tested by the log-rank test[10] before and after adjusting for known prognostic factors. In addition. Cox's multiple regression analysis[11] was performed in order to gain a deeper insight into the role of the putative prognostic variables recorded. The regression coefficients have been estimated by maximum likelihood criterion and their significance was tested by Wald's test[12]

Results

Table 2 shows the main patient characteristics. Primary tumour was located in the lower third of the stomach in 126 of 213 patients (59 per cent) and the majority of patients (154 or 72 per cent) were subjected to subtotal gastrectomy. At histology, 62 per cent of tumours were classified as intestinal. In addition, 124 patients (58 per cent) presented with involvement of the regional lymph nodes (N+) and wall invasion to and beyond the serosa (pT3–4) was documented in 48 per cent of patients.

As far as treatment subgroups are concerned, there was a good balance with regard to sex, age, nodes, histological type, invasion of the wall and location of primary tumour, whereas size of primary tumour and surgical treatment were unevenly distributed (*Table 2*).

Survival estimates of the three treatment groups are shown in *Figure 1*. As can be seen, the survival experience of the three subsets was almost superimposable during the entire follow-up and the 5-year survival rate was approximately 50 per cent for each treatment group ($\chi^2 = 0{\cdot}2044$, $P = 0{\cdot}9$). It is worth



Patients at risk	0	12	24	36	48	60	72	84
Surgery (--)	69	60	48	40	33·	29	22	13
Chemotherapy (—)	75	62	46	37	31	28	19	12
Chemo-immunotherapy (····)	69	59	49	35	31	30	23	12

Figure 1 *Survival curves and estimates of patients at risk in the three treatment groups (surgery only, surgery plus chemotherapy, and surgery plus chemo- and immunotherapy) over the complete follow-up period*

Table 3 *Overall univariate analysis*

Variable	χ^2	d f	*P*
Sex (male, female)	0·16	1	0·69
Age (<60, >60)	2·05	1	0·15
Nodal status (N+, N−)	21·88	1	<0·0001
Invasion of the wall (pT1, pT2, pT3–4)	25·81	2	<0·0001
Size of primary (<3 cm, 3–6, >6)	6·10	2	0·047
Histological type (intestinal, diffuse, mixed)	1·99	2	0·37
Location (upper, middle, lower third, other)	22·43	3	<0·0001

Table 4 *Log-rank test and log-rank test adjusted for relevant prognostic factors*

Variable	χ^2	d.f.	*P*
Treatment (arm 1, 2, 3)	0·20	2	0·90
Treatment adjusted for			
Invasion of the wall + nodes	0·28	2	0·87
Invasion of the wall	0·25	2	0·88
Nodal status	0·30	2	0·86
Age	0·20	2	0·90
Histological type	0·24	2	0·88
Location of primary	0·43	2	0·80
Size	0·70	2	0·70

mentioning here that, as it will be reported later, major deviations from adjuvant treatment administration were documented.

The univariate analysis which aimed to investigate the role of prognostic variables was carried out on the entire series of evaluable patients. The results are reported in *Table 3*. Regional nodal status, depth of wall invasion and location of primary tumour were the single factors which affected survival outcome.

To investigate whether any clinical or histological variable could have affected overall treatment outcome, an adjusted procedure was utilized. *Table 4* clearly shows that no treatment effect was evident even after adjustment for major prognostic variables. Since type of surgery was only moderately balanced within the three treatment subgroups, an analysis of treatment effect adjusted for surgery was also performed. The results clearly indicated that treatment outcome was not influenced by type of gastrectomy ($\chi^2 = 0{\cdot}63$, d.f. = 2, $P = 0{\cdot}73$).

Cox's regression analysis was carried out by resorting to a backward procedure; all the independent variables were inserted in the initial model and results concerning the final model are reported in *Table 5*. Regional lymph node involvement as well as degree of wall invasion beyond the mucosa adversely affected survival. Similarly, location of primary tumour influenced final results, the upper third appearing to be the less favourable from a prognostic point of view. No other variable was found to be statistically significant.

Table 5 *Maximum likelihood estimate of coefficients (β) obtained by final model of Cox's regression analysis, their standard deviations and significance level of Wald's statistics*

Variable		β	s d.	*P*
Nodal status	N−	0		
	N+	0·8342	0·2293	0·0003
Wall invasion	pT1	0		
	pT2	0·8383	0·4003	0·0362
	pT3–4	1·1385	0·3914	0·0036
Location	Upper third	0		
	Lower third	−1·3948	0·3376	0·000037
	Middle third	−1·3440	0·3955	0·0007
	Other	−0·9305	0·3664	0·0111

N−, absence of involved regional nodes, N+, presence of involved regional nodes

Treatment tolerance and follow-up

In patients allocated to adjuvant treatments, bone marrow suppression was the dose-limiting toxicity and therapy had to be discontinued in 12 patients (CT 6; CT + IT 6). Two patients died from marrow aplasia: one had been allocated to CT 3 months after surgery and the other to CT + IT 64 months after surgical resection. However, in the majority of cases adjuvant treatment had to be discontinued either because of patient refusal or because of the cautious attitude taken by the treating physicians.

Table 6 *Current adjuvant trials in curatively resected gastric cancer*

GITSG[13]	Curative resection	No further treatment
		FU 325 mg/m^2 days 1–5 q 10 weeks and Me-CCNU 150 mg/m^2 p.o. day 1 repeated every 10 weeks
VASOG[14]	Curative resection	No further treatment
		FU 9 mg/kg i.v. days 1–5 every 7 weeks and Me-CCNU 4 mg/kg day 1 repeated every 7 weeks
ECOG[15]	Curative resection	No further treatment
		FU 325 mg/m^2 i.v. days 1–5 FU 325 mg/m^2 i.v. days 36–40 and Me-CCNU 150 mg/m^2 p.o. day 1 repeated every 10 weeks
Schlag *et al* [16]	Curative resection	No further treatment
		FU 10 mg/kg i.v. days 1–5 BCNU 40 mg/kg i.v. days 1–5 repeated every 8 weeks

GITSG, Gastrointestinal Tumor Study Group; VASOG, Veterans Administration Surgical Oncology Group; ECOG, Eastern Cooperative Oncology Group, FU, 5-fluorouracil, Me-CCNU, semustine, BCNU, carmustine

All patients receiving adjuvant therapy complained of gastrointestinal disturbances; in four of them (CT 3; CT + IT 1) they were recorded as severe and necessitated discontinuation of treatment. Treatment was discontinued in another 12 patients (CT 5; CT + IT 7) because of hepatitis or other concomitant diseases. Finally, 17 patients (CT 11; CT + IT 6) refused to complete the adjuvant programme mainly for psychological reasons.

Overall, a total of 18 patients, including the 2 cases of marrow aplasia, died without clinical and radiological evidence of disease progression (S 2; CT 8; CT + IT 8). Autopsy was carried out in only one patient and showed tumour involvement of the pancreatic nodes. It is worth noting that many of these patients were aged over 60 years at the time of tumour diagnosis.

Discussion

The design of the present study was discussed among participating centres in 1976 and the trial was activated in March 1977. Adjuvant treatment was essentially based on a similar regimen to that reported by the ECOG group to have obtained improved results in advanced gastric cancer[4]. The fact that a nitrosourea derivative in association with an antimetabolite was effective in palliative treatment of advanced disease prompted many investigators to test similar combinations as adjuvant treatments following curative resections. *Table 6* illustrates the regimens utilized by other research groups. As can be seen, there are no major differences in the chemotherapy regimens compared with our own, even if in one study BCNU was utilized instead of Me-CCNU. Our findings are in agreement with those reported by VASOG, ECOG and a German trial[14–16] and show no benefit on survival from the addition of adjuvant chemotherapy (with or without immunotherapy) to curative surgical resection. The only exception is the Gastrointestinal Tumor Study Group (GITSG) who reported a statistically significant survival improvement favouring adjuvant treatment after adjusting for important covariates[13].

The results of the present study were not totally unexpected. First of all, in advanced disease subsequent studies failed to confirm the initial favourable remission rate and survival from combination chemotherapy with Me-CCNU and FU[5]. In addition, the initial studies which were activated around the 1970s and utilized single agent chemotherapy showed some controversial results. In fact, benefit from adjuvant chemotherapy was essentially reported from Japanese studies and it should be kept in mind that diagnosis of stomach cancer in Japan is generally made at an earlier stage than in western countries so that a different biological behaviour cannot be entirely ruled out[3].

Levamisole, having been used in a variety of solid tumours, is no longer employed essentially because long-term results have failed to substantiate favourable preliminary findings. Our experience confirms the lack of effect from levamisole when administered in combination with adjuvant chemotherapy.

In the light of present results, chemotherapy with Me-CCNU and FU cannot be recommended as adjuvant treatment in gastric cancer[17]. In addition, the chemotherapy regimen as administered in this protocol caused clinically important patient discomfort and two patients died from bone marrow aplasia. It should be noted that nitrosoureas, particularly Me-CCNU, may potentially induce leukaemia. Boice *et al.*[18] evaluated the risk of leukaemia complications in patients with gastrointestinal cancer who were treated in nine randomized clinical trials and documented 17 leukaemic disorders among 2067 patients given Me-CCNU as adjuvant therapy, but in only 1 of 1566 patients given a non-nitrosourea therapy.

Despite the fact that regimens with Me-CCNU and FU cannot be recommended for adjuvant treatment in patients with gastric cancer, it should be remembered that approximately 50 per cent of our patients died within 5 years from curative surgical resection. Therefore, some form of adjuvant treatment, either a different regimen or an alternative modality, is needed to improve disease-free and overall survival. Current adjuvant studies utilize Adriamycin†-containing regimens but definitive results are not yet available[19]. Future trials should also be designed after identification of high risk patients. In fact, multivariate analysis of our present series has mainly confirmed previous findings from a retrospective evaluation carried out on a historical group of 400 patients subjected to curative resection at the Istituto Nazionale Tumori of Milan[20]. Regional lymph node status, depth of wall invasion at histology and location of primary tumour were able to affect survival irrespective of adjuvant therapy. Adequate identification of patients curable by surgery alone will result in sparing unnecessary and potentially toxic treatments. In patients not curable by surgery, future trials should include potentially more effective drugs or new routes of drug administration (e.g intraperitoneal administration) or alternative treatment modalities. In addition, adjuvant trials following curative resections of gastric cancer should include a no-treatment control as well as careful surgical and pathological staging.

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† *Adriamycin is produced by Farmitalia Carlo Erba Ltd*

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Appendix

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Surgical aspects of a district hospital combined gastroenterology clinic

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The surgical aspects of 12 years' involvement with a combined consultative gastroenterology clinic at a district general hospital are reviewed. In this time the overall number of patients subjected to surgery has gradually fallen and the average age of patient referral has gradually increased and the logistical implications are considered. Trends for the common diagnoses encountered are discussed and the educational benefit of the clinic is stressed.

Keywords: Gastroenterology, combined clinic, surgical aspects

Gastroenterology is a specialty which particularly lends itself to a multidisciplinary approach[1]. Working in a district general hospital with a modest catchment population of approximately 190 000, the creation of a fully integrated in-patient unit for gastroenterological problems seemed an unrealistic proposition and our local solution at the beginning of 1973 was to launch a combined consultative out-patient clinic for gastroenterological problems with contributions from physician, surgeon and radiologist. This required nothing for its establishment other than the enthusiasm and co-operation of all parties and the project was made easier by the fact that the physician and surgeon already had a simultaneous out-patient clinic. Referrals were sought from both general practitioners and within the hospital, the main aim being to improve clinical management by minimizing the number of hospital visits the patient had to make, planning an appropriate sequence of investigations, and adding the patient's name directly to the waiting list if surgery seemed appropriate. The clinic is now held three times a month. Each patient is seen by either the physician or the surgeon both working from the same consulting suite, although the initial clerking is often done by the junior staff. Particular emphasis is placed on thorough clinical assessment in order to make a working diagnosis with the minimum of specialized investigations. At the end of the morning the clinical staff are joined by a radiologist for a joint discussion, each case being presented and available X-rays reviewed. A provisional diagnosis is suggested and a combined decision is then made about an appropriate course of action.

Additional clinic benefits have been the establishment of a data base which has been used frequently for clinically oriented research projects and the clinic session, although essentially a service commitment, has proved to have a very useful educational value which the junior staff (surgical and medical) have much appreciated

An account of the clinic's operation and analysis of the first year's workload was reported in 1975[2]; since then referrals have continued unabated. We have recently completed an analysis of new patients seen in the combined gastroenterology clinic for the 12-year period 1973–1984[3] and using this data we were interested to assess the impact of the workload on the clinic surgeon (one of a team of four general surgeons at the Cumberland Infirmary) and to identify any trends and changes in surgical practice.

Patients and methods

All new referrals seen in the combined gastroenterology clinic for the 12-year period 1973–1984 have been included. There has been no significant change in the population size served by the district (190 000) and no major alteration in referral pattern during this time. Likewise the number of general surgeons at the Cumberland Infirmary has remained constant. Details of the patients age, sex, diagnoses and whether or not surgical intervention was required have been obtained from the diagnostic index maintained since the clinic's inception The final diagnosis has been taken as that made after appropriate investigations and follow-up have been completed.

Results

A total of 4362 patients have been seen during the 12-year period (2346 females and 2016 males). The average age was 52 years (range 10–95 years). The number of patients in each diagnostic category for successive 4-year periods is shown in *Table 1*. Because more than one diagnosis is recorded when a patient with multiple pathology is encountered, the total number of patients with each diagnosis recorded is greater than the total number of patients referred

The operation rate has fallen steadily from >35 per cent in 1973 to 20 per cent in 1984 (*Figure 1*) while the percentage of patients aged 65 years and over subjected to surgery has gradually increased. The reduction in operation rate has largely been accounted for by the decline in surgery for duodenal ulceration, gastro-oesophageal reflux and hiatus hernia, and diverticular disease of the colon

The number of cases of biliary tract disease has fluctuated but the percentage operated on has remained high, only falling below 80 per cent in 2 of the 12 years, thus making biliary tract disease (and gallstones in particular) the biggest single contributor to the surgical workload over the survey period.

Carcinoma of the stomach and oesophagus accounted for 2 per cent of total cases and 74 per cent of these underwent surgery. Colorectal carcinoma accounted for 3 per cent of cases, 94 per cent being subjected to operation. Including carcinoma of the pancreas, a total of 228 patients with gastrointestinal malignancy were referred, 192 (84 per cent) being subjected to surgery. Of those undergoing surgical intervention for malignancy 52 per cent were aged 65 years or over, emphasizing the contribution of the elderly to the surgical workload.

Idiopathic proctocolitis accounted for 3 per cent of cases with only 4 per cent undergoing surgery and little change in referral pattern or operation rate is apparent over the 12-year period. Crohn's disease accounted for <1 per cent of cases but just over half underwent surgery at some stage.

It should be noted that the largest single diagnostic group was disturbances of gastrointestinal function, comprising 33 per cent of total referrals. As expected these patients made a negligible contribution to the surgical workload.

Discussion

The gradual fall in operation rate of patients referred to the gastroenterology clinic during the survey period has not

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Table 1 *Diagnostic breakdown and number undergoing surgical intervention for successive 4-year periods*

Years Patients	1973–76 ($n = 1546$)		1977–80 ($n = 1297$)		1981–84 ($n = 1519$)		Grand total ($n = 4362$)	
Diagnostic category	No of referrals	Surgical intervention	No. of referrals	Surgical intervention	No of referrals	Surgical intervention	No. of referrals	Surgical intervention
Oesophageal								
Gastro-oesophageal reflux	142	41	177	34	183	30	502	105
Carcinoma	9	5	9	7	12	6	30	18
Achalasia	2	2	2	2	1	1	5	5
Gastric lesions								
Benign ulcer	47	13	52	20	49	11	148	44
Carcinoma (including lymphoma)	31	27	20	16	23	16	74	59
Combined GU + DU	17	13	13	6	12	7	42	26
Duodenal ulcer	253	148	156	65	159	55	568	268
Dyspepsia after previous gastric surgery	55	8	44	6	62	5	161	19
Functional dyspepsia	201	2	173	1	157	0	531	3
Biliary tract disease	170	151	117	101	141	112	428	364
Pancreatic disease								
Chronic pancreatitis	9	3	5	4	5	2	19	9
Carcinoma	5	4	0	0	3	2	8	6
Coeliac disease	5	0	0	0	2	0	7	0
Crohn's disease								
Small gut	4	4	2	0	7	3	13	7
Colonic	8	7	6	1	0	0	14	8
Combined	4	3	2	1	3	1	9	5
Colorectal disorders								
Carcinoma	38	36	30	28	48	45	116	109
Diverticular disease	101	16	115	12	144	5	360	33
Proctocolitis	52	4	44	2	44	0	140	6
Irritable bowel syndrome	214	4	189	2	241	0	644	6
Simple constipation	43	1	44	0	27	0	114	1
Anal lesions	26	4	55	10	73	16	154	30
Psychiatric disorders	111	0	54	0	33	0	198	0
Miscellaneous								
Gastroenterological	96	10	100	15	142	30	338	55
Non-gastroenterological	70	8	52	6	75	14	197	28
Drugs	12	0	11	0	15	0	38	0
Alcohol	28	0	26	0	28	0	82	0

GU, gastric ulcer; DU, duodenal ulcer

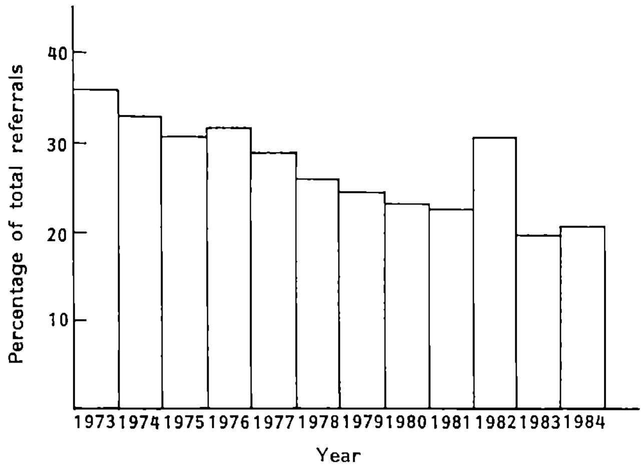

Figure 1 *Percentage of total referrals subjected to surgery*

resulted in any lessening of the overall workload of the clinic surgeon. In addition to his gastroenterology clinic involvement he has also taken his full share of emergency admissions, run general surgical clinics in which he also saw gastroenterology patients and dealt with inter-hospital referrals. It should also be emphasized that the combined gastroenterology clinic serves as a 'trouble-shooting forum' for the general practitioner and the more obvious and potentially urgent gastrointestinal problems are sometimes admitted directly to the ward, bypassing the clinic and thus being excluded from the diagnostic index. This applies particularly to rapidly progressive dysphagia due to upper gastrointestinal malignancy (accounting for approximately six patients a year over the last 3 years) so that patients with carcinoma of the oesophagus or stomach are slightly under-represented in the diagnostic breakdown.

Despite this gradual fall in operation rate, the combined gastroenterology clinic still makes a very significant contribution to the surgical workload. Surgery for gastrointestinal malignancy, in particular, is time consuming, requiring careful pre- and postoperative assessment and in addition the age of the patients contributed to an increasingly heavy burden for the nursing staff and also delayed throughput. Also the amount of theatre time required for resection procedures has led to an inevitable build up of the waiting lists for less urgent surgical problems.

The increasing age of the patients referred to the clinic has caused concern with respect to nurse staffing levels in the clinic itself and in the surgical wards, and has led to logistical problems in the radiology department[4]. During the survey period the number of patients referred aged 65 years and over was 1061 (636 females, 425 males), comprising 24 per cent of the total referrals The diagnostic categories in which elderly patients had an increased representation were gastrointestinal malignancy (oesophagus, stomach, pancreas and colorectum) and diverticular disease of the colon. Conditions which were seen with approximately the same frequency in the elderly population as in the total referral group included gastro-oesophageal reflux, gastric ulceration and biliary tract disease. The diagnostic categories in which the elderly were strikingly less frequently represented in the total population group comprised functional gastrointestinal problems. This group included patients with functional dyspepsia and the irritable bowel syndrome but simple constipation was an exception in that it had an increased representation. The percentage of the elderly groups submitted to surgical intervention did not differ from the total population studied[4].

The surgical trends identified confirm the previously held impression that fewer patients with duodenal ulceration have been subjected to elective surgical intervention during the survey period and fewer patients with this diagnosis are referred. This may reflect a higher standard of general practitioner training and greater availability of open access diagnostic facilities. Likewise the declining operation rate may have been accelerated by the introduction of H_2 antagonists, although the trend had already been set before their introduction. The figures show our conservative approach to gastro-oesophageal reflux and conversely the tendency to treat gallstones surgically, with medical therapy as yet contributing very little in this field. Patients referred with diverticular disease of the colon have rarely needed elective surgical intervention and likewise 96 per cent of those referred with proctocolitis were successfully managed medically.

The broad case mix referred to our integrated medico-surgical gastroenterology clinic has been appreciated by the junior surgical staff. Senior registrars, registrars and senior house officers have been involved over the years and have realised the importance of a thorough clinical assessment including social, drug and alcohol histories They have become aware of the high incidence of functional gastroenterological problems and the importance of age, the incidence of organic disease increasing sharply in the older age group. The junior staff attending from the medical department have had a much greater exposure to surgical gastroenterology than they would have obtained from attending exclusively 'medical' gastroenterology clinics.

The continued attendance of a radiologist during the patient discussion has been of great benefit to review the results of previous radiological procedures and to plan an appropriate sequence of further investigations if necessary. The presence of a physician may lead to the avoidance of unnecessary surgery and conversely he can be stopped from procrastinating when surgical intervention is patently necessary.

In conclusion, there would seem to be no losers from the introduction of this venture. The patients undoubtedly benefit from a firm plan of action being drawn up at their first visit with a consequent acceleration of the diagnostic process. The attempt to reduce the times a patient has to return to hospital is particularly important in a predominantly rural area such as ours where long distances may be involved as public transport is at a premium and ambulance journeys are expensive.

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Total duodenal diversion in the treatment of complicated peptic oesophagitis

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Total duodenal diversion (TDD) has been carried out in 59 patients with complicated forms of peptic oesophagitis (acquired short oesophagus, columnar lined oesophagus, previous oesophagogastric surgery, stenosis). A standard procedure (truncal vagotomy, antrectomy and gastrojejunal anatomosis using a 70 cm Roux-en-Y loop) was performed in 41 patients, and some technical adjustments were required in 18 patients previously operated on. One patient died from postoperative pulmonary embolism. Bowel movements were resumed before the fifth postoperative day in 93 per cent of patients (54/59). Early postoperative complications (gastroparesis, 5; fistula, 1; subsequent operation, 1) occurred in 12 per cent of patients. Stabilization of the oesophagitis was achieved in less than 3 months in 95 per cent of cases (55/58). There were two cases of regression of columnar lined oesophagus. A 3-h postprandial pH assessment showed that the reflux had been controlled in 92 per cent of cases (47/51). One patient who still had an acid reflux died subsequently of a perforated oesophageal ulcer. Three anastomotic ulcers occurred in eight patients who did not have vagotomy. Digestive side-effects have been observed in nine patients, but only in one case were they crippling. Our results suggest that TDD is a suitable form of treatment for complicated forms of peptic oesophagitis.

Keywords: Total duodenal diversion, complicated oesophagitis

Vagotomy and antrectomy is an effective method of reducing gastric acid secretion, and when combined with a Roux-en-Y gastrojejunal anastomosis, biliary and pancreatic secretions are diverted away from the stomach. This procedure of total duodenal diversion (TDD) also has an indirect benefit on gastro-oesophageal reflux and was first tried for the treatment of oesophagitis induced by alkaline reflux following proximal oesophagogastrectomy[1]. Its indications have been extended to the treatment of complicated forms of oesophagitis, where it is an alternative to an antireflux procedure or oesophagogastric resection. The present study sets out the results of a series of 59 TDD operations and defines the indications of the technique.

Patients and methods

Patients

Between 1 January 1979 and 31 December 1986, 103 patients were operated on in our unit for complicated forms of peptic oesophagitis. The complications arose because of the severity of the oesophageal lesion (stenosis, ulcer, acquired short oesophagus, columnar lined oesophagus) or because of previous surgery (Heller's myotomy, oesophagogastric resection, or surgery for hiatal hernia). Of the 103 patients 59 (45 men and 14 women) aged from 25 to 70 years were treated by TDD. The type of lesions present in these patients is shown in *Table 1*. In 33 cases there had been a previous surgical procedure. In the case of hiatal repair, all patients had had two or three operations and TDD was performed when, after intra-operative evaluation, it was not possible to perform a satisfactory antireflux procedure. We did not perform TDD simply for recurrence of oesophagitis following a primary hiatal hernia repair. In our experience such recurrence was associated with a technical deficiency and it was possible to do a further antireflux procedure. Oesophageal stenosis was graded by the ability to pass an endoscope of 9 or 11 mm in diameter. Our definition of acquired short oesophagus is based on an intra-operative diagnosis when the oesophagogastric junction cannot be brought down sufficiently into the abdomen to perform an effective fundoplication. Of the 21 patients with columnar lined oesophagus (i.e. circumferential columnar epithelium extending for more than 3 cm) without dysplasia who were operated on by TDD, haematemesis had been observed in two patients with Barrett ulcers and in one with an oesophageal ulcer following a proximal oesophagogastrectomy.

A pre-operative pH study was performed in 41 patients. Oesophageal pH was recorded continuously during 3 h after a test meal. Patients were in a sitting position during the first and third hour and in a supine position during the second hour. Results were expressed quantitatively by a score based on the duration and severity of reflux periods, the normal value of the score was <90 (References 2 and 3).

Methods

The operation was performed through an abdominal approach and involved truncal vagotomy and antrectomy, with resection of the mobile section of the first part of the duodenum, and of the stomach below a vertical line extended from the angle of the lesser curvature. The duodenal stump was closed using a stapler. An end-to-side gastrojejunal anastomosis was then constructed using a 70 cm Roux-en-Y loop (except in one case in which an end-to-end anastomosis was used).

Table 1 *Nature of lesions and previous operations in 59 patients undergoing total duodenal diversion*

	No. of patients
Stricture (length)	
<9 mm	6
9–11 mm	9
>11 mm	6
Acquired short oesophagus	7
Columnar lined oesophagus	21
Previous oesophagogastric surgery	
Antireflux surgery	16
Heller's myotomy	10
Oesophagogastric resection	5
Vagotomy–pyloroplasty	1
Vagotomy–antrectomy	1
Total	82*

*Some patients had two or more associated causes for complicated peptic oesophagitis

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Whenever technically possible, the diaphragmatic crura were sutured together behind the oesophagus using non-absorbable material. This standard procedure was carried out in 41 cases. In 33 patients sutures were placed between the left side of the oesophagus and the fundus of the stomach. A more extensive antireflux manoeuvre was used in eight patients. Various technical modifications were used in the remaining 18 patients, namely: vagotomy through a left thoracotomy because of a previous Heller's procedure ($n=3$); two-thirds gastrectomy in place of vagotomy and antrectomy after a Heller's myotomy ($n=7$) and after a previous vagotomy-antrectomy ($n=1$), and antrectomy alone when vagotomy had been performed previously ($n=7$). A nasogastric tube was inserted in all cases. On the seventh postoperative day, all patients were submitted to a radiological study using a water-soluble contrast medium to assess gastric emptying. In patients with stenosis, pre-operative ($n=13$) and/or peroperative ($n=13$) dilatations using bougies were used in conjunction with TDD Long-term surveillance was focused on the evolution of the oesophagitis and on any digestive disturbances (gastric emptying, diarrhoea, dumping) Three months after TDD, all patients were submitted to a barium meal examination and endoscopy. All patients with more than a 1-year follow-up had a second endoscopy Postprandial 3-h pH monitoring was performed in 51 patients, between the third and sixth month after TDD

In cases with a columnar lined oesophagus, endoscopy was repeated at least once a year, with assessment of the length of the lesion and multiple biopsy

Results

The follow-up period ranged from 6 to 96 months (mean 36 months). One patient (2 per cent) with a columnar lined oesophagus died in the postoperative period from pulmonary embolism, confirmed by autopsy One other patient treated for major acid reflux following proximal oesophagogastric resection by left thoracotomy with an intrathoracic anastomosis died 18 months after TDD because of perforation of a peptic ulcer of the thoracic part of the oesophagus. The serum gastrin level was normal, but no secretion tests were performed.

Early complications occurred in seven patients (12 per cent). One minor duodenal fistula healed without further procedure. Bowel action recovered before the fifth postoperative day, except in five patients in whom gastric paresis led to prolonged (7–30 days) gastric suction. The patient with the end-to-end gastrojejunal anastomosis required reoperation 3 months later for gastrojejunal intussusception.

Heartburn disappeared completely in all patients after the immediate postoperative period. In the 21 patients with stenosis, dysphagia was cured without recourse to postoperative dilatation in 18 cases, and following one session of dilatation in 2. One patient with a narrow (less than 9 mm) stenosis had to be submitted to six dilatation sessions. No patient complained of biliary vomiting. Endoscopy showed that peptic oesophagitis, whatever its initial severity, healed within 3 months, except in 2 patients (3·5 per cent of 57 surviving patients) in whom ulceration was still found in the last centimetres of the oesophagus. One of these patients had undergone a gastrectomy without vagotomy following a Heller's procedure. The other patient had already undergone operation on four occasions and had been treated by antrectomy without vagotomy. The two patients with Barrett ulcers and the one patient with oesophageal ulceration which had induced pre-operative haemorrhage all showed ulcer healing. Endoscopy showed no bile in the gastric stump of all patients and the mucosa was pink with no sign of inflammation. Among the 21 patients with columnar lined oesophagus, two cases of regression were observed although dysplasia or adenocarcinoma was not noted.

The mean score of pre-operative pH studies was 180 (range 110–888). The findings of 51 postoperative pH studies were as follows: <90 in 40 patients (78 per cent); >90 and <120 in 7 patients, but without the pH falling below 4 and without reflux episodes of more than 5 min (oesophageal clearance was altered in 2 of these patients); and >500 in 4 patients. Three of these last few patients had been treated by a two-thirds gastrectomy without vagotomy following a Heller's myotomy and oesophageal clearance was altered in two of them. Finally, acid reflux had been present in the deceased patient mentioned above. In the subgroup of eight patients who underwent an antireflux procedure in conjunction with TDD, seven postoperative pH studies were performed and always showed a score of <90.

Significant late complications were observed in 4 of the 57 patients (7 per cent). An anastomotic ulcer occurred in three of the seven patients submitted to gastric resection without vagotomy, following a Heller's procedure. Gastrointestinal sequelae were crippling in one patient (2 per cent) who had been treated for oesophagitis (following a Heller's procedure) by gastrectomy without vagotomy, and who is still complaining of gastric fullness and dumping 17 months after TDD. Other minor difficulties were observed in eight patients: moderate dumping was noted in two cases; disordered gastric emptying, customary during the first 3 postoperative months, persisted for over a year in five cases (9 per cent); and one patient had irregular bouts of postprandial diarrhoea 34 months after TDD.

The overall failure rate was thus 22 per cent excluding the minor late sequelae. At the end of the current follow-up, 45 of the 59 patients (76 per cent) remain totally asymptomatic.

Discussion

In this series of 59 patients with complicated forms of peptic oesophagitis, TDD provided a rapid and stable regression of the oesophagitis without major digestive dysfunction in most cases. The low postoperative mortality and morbidity rate is in keeping with that noted in several publications[4–8]. The main early postoperative problem is gastroparesis although this is usually temporary[9–12] and significant dumping is rare[6,13,14]. The rerouting of food from the duodenum and proximal jejunum may be implicated when dumping occurs and the incidence of the dumping syndrome may be related to the length of the Roux-en-Y loop[15]. Diarrhoea is seldom noted, and may be related more to the vagotomy than to microbial contamination of the afferent loop or the stump of the Roux-en-Y loop[16]. Healing of oesophagitis, with scarring of ulceration, is usually achieved within a few months of TDD as the operation significantly reduces the various components of reflux, namely acid secretion, bile and pancreatic juice[17,18]. The acid component of the reflux has been shown to be reduced by our pH study, while no bile was found in the gastric stump on endoscopy. We feel that a 70 cm loop is necessary to avoid biliary and pancreatic reflux[19,20]. The stability of the results in terms of gastro-oesphageal reflux is a marked advantage of the procedure when compared with fundoplication and Collis gastroplasty[5,7,14,21].

After several hiatal repairs, local conditions prevent the performance of an efficient antireflux procedure or make for difficulties in the approach of the oesophagogastric junction. Thus we consider TDD preferable, on the one hand, to a further fundoplication with vagotomy and pyloroplasty and, on the other, to an intrathoracic fundoplicaton[14,22]. It has a lower morbidity than the Nissen-type transabdominal fundoplication in patients who have already undergone previous operations, and its results in terms of gastro-oesophageal reflux are better[23]. In cases of reflux following a Heller's myotomy, TDD avoids approaching the hiatal area and obviates the risk of tearing the oesophagus, which may be vulnerable if involved by oesophagitis.

When truncal vagotomy is not practicable through the abdominal approach, a transthoracic or transdiaphragmatic vagotomy seems to be preferable to a more extensive gastric resection[24,25]. Without vagotomy, the incidence of anastomotic ulceration may reach 20 per cent[7,8,26,27].

TDD is particularly indicated for the treatment of gastro-oesophageal reflux following oesophagogastric resection, all the more because the reflux may be mixed or alkaline following pyloroplasty. It avoids a total gastrectomy or coloplasty[28]. The antrectomy must then be done, sparing the blood vessels of the greater curvature in order to ensure vascularization of the gastric stump[29]. Like other authors, we have not encountered gastric necrosis[24] although a simplified pyloric bypass technique without gastric resection has been described in cases with alkaline reflux to reduce that risk[30] TDD also allows the treatment of reflux when oesophagogastric resection has been carried out with colonic interposition, especially in cases of anastomotic cologastric ulceration. Since a shortened oesophagus binds the cardia inside the thorax, reconstruction of an abdominal oesophagus and abdominal fundoplication is impossible in such cases. The intrathoracic Nissen fundoplication carries significant morbidity, notably gastric perforation with its reported mortality rate of 50 per cent[31–34]. This complication is a major factor when considering that procedure which, nevertheless, has an 80 per cent success rate[35]. Extensive transthoracic dissection of the oesophagus associated with an antireflux procedure has a high rate of recurrence which is difficult to treat[36]. We have no experience with the Collis gastroplasty, which is credited with good results in 80 per cent of cases of gastro-oesophageal reflux although the long-term persistence of these results is not confirmed[21] All of these procedures involve a thoracotomy and diaphragmatic incision. In our experience, the quality and stability of the results of TDD in the treatment of acquired short oesophagus lead us to continue to use it, rather than resort to a gastric muff on the upper part of the stomach or a Collis procedure carried out through an abdominal approach[37–39].

The regression of columnar lined oesophagus following an antireflux procedure is still a matter for discussion The quality and persistence of our early results with TDD[40] led us to treat our current 21 patients in this way Our results to date do not allow us to recommend the policy unreservedly though gastro-oesophageal relux is more severe in such patients[41]. The reduction of risk of adenocarcinoma following TDD has not been assessed in the literature and further data are required.

Within the spectrum of complicated peptic oesophagitis, stenosis was not in itself an indication for TDD We reserve TDD for patients with dilatable stenoses in whom the cardia cannot be lowered A dilatable stenosis with a lowerable cardia should be treated in our view by partial posterior fundoplication through an abdominal approach, combined with dilatation. Persistent peptic ulcer and stenosis resistant to dilatation are indications for oesophagogastric resection. While we do not feel that TDD is indicated as an initial procedure for the treatment of gastro-oesophageal reflux, it is of interest that a randomized prospective study suggests that TDD gives better results than the Nissen procedure in cases of uncomplicated oesophagitis[42]

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'Collagen overcoat': an approach to haemorrhagic oesophagitis

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Serious life-threatening bleeding from oesophagitis is uncommon although chronic iron deficiency anaemia may develop. Oesophagitis is usually attributed to reflux of gastric acid owing to failure of the lower oesphageal sphincter, which may be associated with an hiatus hernia or brought about by the presence of a nasogastric tube. When haemorrhagic oesophagitis occurs in a ventilated patient following abdominal surgery and prolonged ileus, management can be difficult. Administration of H_2-receptor antagonists may be of benefit, but little help is gained by antacids or liquorice extracts passed down the nasogastric tube

We report a case in which a new technique was used in management, that has not to our knowledge been previously described.

Case report

A 60-year-old man underwent laparotomy for small bowel obstruction where some 50 cm of ileum was found to be gangrenous and was resected. His postoperative course was complicated by gross sepsis, renal failure and prolonged ileus He required ventilatory support. Ten days postoperatively he developed persistent upper gastrointestinal haemorrhage to the extent that on occasions fresh blood and large clots were welling up into his pharynx. At endoscopy bleeding was found to be coming from a very severe, ulcerative, haemorrhagic oesophagitis

Despite having been on intravenous H_2-receptor antagonist therapy, and changing his standard 14FG Ryles tube for a fine 6FG 'Silk' feeding tube down which was passed De-Nol (Brocades Ltd, UK. tripotassium di-citrato bismuthate) liquid, he continued to bleed Repeat endoscopy revealed further progression of his oesophagitis It was felt that injecting sclerosant would not be of benefit and might exacerbate the condition. Similarly, standard balloon tamponade by Sengstaken–Blakemore tube might result in further ulceration and sloughing of the oesophageal epithelium

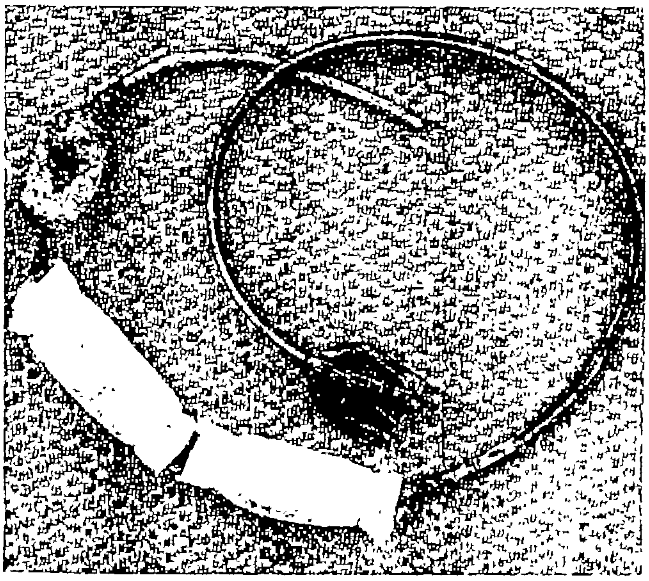

Figure 1 *Sengstaken–Blakemore tube showing the sheets of collagen haemostatic felt encircling the oesophageal balloon*

In order to apply a haemostatic agent to the bleeding areas, two 10 × 12 cm sheets of collagen haemostatic felt (COLLASTYPT, B. Braun Melsungen AG) were rolled around the deflated oesophageal balloon of a Sengstaken–Blakemore tube and secured wth 3/0 plain catgut (*Figure 1*). The ensemble was coated liberally with K-Y Jelly (Johnson and Johnson Ltd, UK) and passed orally so that the 40 cm mark was level with the incisor teeth. Approximately 30 ml of air was introduced into the oesophageal balloon to bring the collagen into contact with the oesophageal wall.

After 72 h, at which time it was felt that the catgut ties should have dissolved and the collagen should have been absorbed, the tube was withdrawn with no sign of collagen, catgut or bleeding. Despite a protracted stay in the intensive care unit, the patient showed no signs of further gastrointestinal haemorrhage.

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Death from undiagnosed peptic ulcer complications: a continuing challenge

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A 10-year study of all 9653 autopsies performed in the Plymouth Health District, UK from 1977 to 1986 revealed 154 patients who died from undiagnosed peptic ulcer complications. In all, 118 of these patients died suddenly at home and 36 died in hospital. Most patients were elderly although 47 were under 70 years and 2 were under 50 years of age. Anti-inflammatory drugs were being used by 81 of these patients, an incidence of 60 per cent where full drug histories were available. Women who died were much more likely to be using these drugs than men. This study emphasizes the hitherto unrecognized importance of death from undiagnosed peptic ulcer disease and further highlights the potential risk of non-steroidal anti-inflammatory drug use.

Keywords: Peptic ulceration, sudden deaths, anti-inflammatory drugs

Peptic ulceration remains a significant cause of mortality in England and Wales, being responsible for nearly 50 000 deaths in the last 10 years[1]. While most deaths from bleeding or perforated ulcer occur in hospital, recent reports have demonstrated the hitherto unrecognized importance of sudden at-home deaths[2–4]. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with peptic ulcer complications[5–10] and it has been suggested that a large proportion of peptic ulcer deaths are related to NSAID use[2].

The aim of this study was primarily to determine the importance of death from undiagnosed peptic ulcer complications in a given area and secondly to determine the relationship of these deaths to NSAID use.

Patients and methods

This study is based on an analysis of all patients undergoing autopsy in the Plymouth Health District, UK in the 10 years 1977–87 inclusive. The population remained steady at 412 000 over this time (Office of Population Censuses and Surveys) The autopsies studied included all 6414 coroner's (5782 out-of-hospital and 632 in-hospital deaths) and 3239 hospital post mortems performed in this period. During this 10-year period approximately 51 000 patients died in the Plymouth area: 18 000 in hospital and 33 000 at home Thus, 3871 of 18 000 (21·5 per cent) hospital deaths and 5782 of 33 000 (17·5 per cent) home deaths underwent autopsy Those patients where the cause of death was considered by the pathologist to be from bleeding or perforated benign peptic ulcer were studied further All autopsy reports were closely scrutinized by the authors and the nature of the ulcer and complication was recorded, as was information on other significant medical disease.

Patients who died suddenly at home all underwent coroner's autopsy and in these cases a drug and medical history was obtained whenever possible from the general practitioner records (Devon Family Practitioner Committee) or from the coroner's own records. Particular reference was made to the use of NSAIDs and this excluded the use of aspirin. No attempt was made to determine the dosage or length of time of use of NSAIDs for at-home deaths. Patients who died in hospital underwent either a coroner's or hospital autopsy and in these cases hospital case records were examined to obtain a drug and medical history

Only those patients who died from unsuspected peptic ulcer complications, after careful scrutiny of hospital and general practitioner records, were included in this report. Statistical analysis, where indicated, was by means of χ^2 test.

Results

Analysis of all autopsy reports revealed 118 at-home deaths and 36 hospital deaths from unsuspected peptic ulcer complications. The number of patients from each year of the study is shown in *Table 1*. Of the 118 at-home deaths 66 were women (median age 77, range 54–94) and 52 men (median age 73, range 46–93). Of the 36 hospital deaths 16 were women (median age 80, range 62–85) and 20 men (median age 72, range 65–91). Of the patients who died at home 38 were under the age of 70 years and 2 were under 50 years. Nine patients who died in hospital were under 70 years. Ten patients who died at home and six who died in hospital had co-existent carcinomatosis, although the final cause of death was a peptic ulcer complication.

The sites of peptic ulceration and complication for at-home and hospital deaths are shown in *Table 2*. The use of NSAIDs by these patients is shown in *Table 1*. Accurate records were not always available for at-home deaths and this was particularly so in the 1977–81 period when many had been destroyed. Of the 118 patients who died at home 61 (51·7 per cent) were using a NSAID and in 15 (12·7 per cent) cases no information on drug use was available. NSAIDs were therefore being used by 59·2 per cent of patients in whom a drug history was obtained. Similarly of the 36 patients who died in hospital 20 (56 per cent) were using NSAID and in 4 (11 per cent) cases no drug history could be found. NSAIDs were therefore being used by 62 per cent of patients in whom a drug history was available. For patients who died at home, NSAIDs were prescribed for rheumatoid arthritis in 14, oesto-arthritis in 21, other 'rheumatic' conditions in 10 and for no obvious reason in 16. For patients who died in hospital the corresponding figures were rheumatoid arthritis in five, osteo-arthritis in eight, other 'rheumatic' conditions in three and no obvious reason in four. Seven patients who died at home and three in hospital were also using steroids. The individual NSAIDs are listed in *Table 3* The dosage of drugs for patients who died in hospital was, in each case, that recommended by the manufacturer and the length of time of use varied from 1 month to 3 years. A marked sex difference was noted in the use of NSAIDs. Of 52 men, 16 (31 per cent) who died at home were using NSAIDs in contrast to 45 of 66 women (68 per cent): $\chi^2 = 17·75$, $P < 0·001$. Of 20 men who died in hospital, 7 (35 per cent) were using NSAIDs in contrast to 13 of 16 women (81 per cent); $\chi^2 = 9·69$, $P < 0·01$ Thirteen patients had more than one ulcer. Seven patients had two ulcers: four of these were using NSAIDs; and six patients had three or more ulcers: all were using NSAIDs.

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Table 1 *The number of patients by year and the use of NSAIDs for at-home deaths and for hospital deaths*

	At-home deaths				Hospital deaths			
Year	Number of patients	NSAIDs	No NSAIDs	Unknown	Number of patients	NSAIDs	No NSAIDs	Unknown
1977	6	1	1	4	3	—	2	2
1978	6	1	3	2	3	1	2	—
1979	10	5	4	1	3	2	—	—
1980	14	6	5	3	2	1	—	1
1981	16	8	5	3	4	2	1	1
1982	14	9	4	1	5	3	2	—
1983	12	7	4	1	4	3	1	—
1984	19	11	8	—	5	4	1	—
1985	9	6	3	—	3	2	1	—
1986	12	7	5	—	4	2	2	—
Total	118	61	42	15	36	20	12	4

NSAID, non-steroidal anti-inflammatory drug

Table 2 *Peptic ulcer complications in at-home deaths ($n=118$) and in hospital deaths ($n=36$)*

	Bleed	Perforation	Both
At-home deaths			
Gastric ulcer ($n=43$)	23	20	—
Duodenal ulcer ($n=71$)	26	44	1
Other* ($n=4$)	4	—	—
Total	53	64	1
Hospital deaths			
Gastric ulcer ($n=14$)	7	7	
Duodenal ulcer ($n=22$)	9	13	
Total	16	20	

* Other includes oesophageal ulcer 3, stomal ulcer 1

Table 3 *The use of individual non-steroidal anti-inflammatory drugs*

Drug	At-home deaths ($n=61$)	Hospital deaths ($n=20$)
Indomethacin	16†	7*
Piroxicam	12*	4*
Naproxen	5*	2*
Ibuprofen	6*	2
Phenylbutazone (W)	6*	2
Ketoprofen	4*	2
Diclofenac	2	—
Diflunisal	2	—
Azapropazone	2	1
Indoprofen (W)	2	—
Benoxaprofen (W)	2	—
Flurbiprofen	1	—
Oxyphenbutazone (W)	1	—

* One patient was also using steroids; † two patients were also using steroids; W, drugs withdrawn from the market

Discussion

Approximately 4500 patients die every year from peptic ulceration in England and Wales[1,11] and, although this total number has remained constant over the last decade, there has been an increase in the number of deaths in women and a corresponding fall in the number in men. These figures are similar to the annual death rate from self-poisoning of 4000 per year, of which less than one-fifth occur in hospital[12]. While most peptic ulcer deaths occur in hospital, this study has shown that a significant number of patients die at home from unsuspected and potentially preventable peptic ulcer complications. Furthermore, the number of deaths from unsuspected peptic ulcer complications is almost certainly an underestimate as only a minority of patients who die undergo autopsy.

Death from unsuspected peptic ulceration in hospital is documented[13,14] although until recently[2–4] the importance of deaths occurring at home was unrecognized. In this study most patients who died from undiagnosed peptic ulceration were elderly although a considerable number were under 70 years with two being in their forties. The provisional causes of death in these patients were extremely varied and great care was therefore taken to include only those patients with unsuspected peptic ulcer complications. This study was by its nature retrospective and although we are unable to comment on prior symptoms, the use of alcohol or smoking habits, most patients who died at home had not consulted their general practitioner with ulcer symptoms. The fact that asymptomatic ulcers are increasingly common with advancing age and that elderly patients are generally less able to tolerate a sudden perforation or massive bleed[14–17] may explain these observations. Furthermore, it has been reported that one-third of the cases of perforated peptic ulcer and one-fifth of gastrointestinal haemorrhage occur in people without any previous symptoms[17].

Recent epidemiological studies have identified an increase in perforated ulcers in elderly women and an increase in bleeding ulcers in both men and women over 60 years of age[18–20]. It has been suggested that the steady increase in the use of NSAIDs, which now account for 24×10^6 prescriptions annually in the UK, is responsible for these changes[2,5–7]. It is also noteworthy that a recent report[2] showed that 60 per cent of life-threatening complications and 80 per cent of all ulcer deaths were associated with NSAID use. In contrast, however, Henry and colleagues found no relationship between fatal peptic ulcer complications and the use of NSAIDs in a case control study from Australia[21]. The Committee on the Safety of Medicines has reported over 600 deaths up to 1985 due to peptic ulcer complications which have been closely related to the use of NSAIDs and roughly 90 per cent of these fatal events were in people aged 60 or over[10]. In the present study 59·2 per cent of at-home deaths and 62 per cent of hospital deaths were associated with the use of an anti-inflammatory agent although it must be emphasized that drug histories were often unavailable for patients dying at home in the first 5-year period. Furthermore, as this study does not include a case control group, no firm conclusions on the risks of individual NSAIDs can be made and such data require a carefully controlled prospective analysis. The problem may be further compounded by the use of over-the-counter drugs such as aspirin and ibuprofen. Women who died from ulcer complications were much more likely to be using a NSAID and although the reason for this sex difference is unclear it has been previously noted[2,5].

What can be done to avoid death from undiagnosed peptic ulcer complications? As most patients who died at home did not seek medical help, an attempt must be made to alter the pathogenesis of the ulcer. We and others would suggest great caution and avoidance, whenever possible, in the use of NSAIDs, especially in the elderly with repeat prescriptions[2,8,22–24]. Simple analgesics should be tried as an alternative and when necessary a reduced dosage of NSAID prescribed in patients over 70 years of age. All prescribers must be knowledgeable of the potential hazards of NSAIDs, even if each individual doctor will only see an ulcer complication every few years. Regarding patients who died in hospital from unsuspected peptic ulcer complications, there must be a heightened awareness of asymptomatic ulcers. All doctors must remember that bleeding or perforated ulcers are potentially curable at all ages by judicious surgery.

This study has highlighted the number of patients who are dying from unrecognized complications of peptic ulceration and the figures presented probably represent only the tip of the iceberg. Most patients, particularly women, who died from unsuspected ulcer complications were using an anti-inflammatory drug and this study provides further evidence for the potential hazards of NSAID use.

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Multivariate approach for assessing the prognosis of clinical oesophageal carcinoma

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We investigated the prognostic contribution of 15 discrete variables on the survival of 123 patients with carcinoma of the oesophagus who underwent oesophagectomy and oesophageal reconstruction. In the mulitvariate analysis, three of fifteen variables were associated with the prognosis of patients who underwent oesophagectomy. The variables are: resectability of the malignant lesion, DNA distribution pattern of the cancer cells and postoperative complications. The DNA distribution pattern proved to be one of the most reliable prognostic factors. These three variables were assigned one of two values, 'favourable' or 'unfavourable', indicative of the effect on survival. The 123 patients were classified into four groups, characterized by eight possible combinations of these three variables. The survival rate of those with two or more 'favourable' variables was the highest, that is about 50 per cent at 5 years after surgery. On the other hand, patients with two or more 'unfavourable' variables had a very poor prognosis. Therefore, early detection and postoperative care play key roles in determining the survival of patients with oesophageal carcinoma.

Keywords: Oesophageal carcinoma, multivariate analysis, DNA pattern

The prognosis of patients with oesophageal carcinoma relates to the stage of the carcinoma, resectability, general condition of the patient, and other factors[1–4]. As these factors are often inter-related, a simultaneous multivariate analysis[5] should help to assess the prognosis. We have thus used a multivariate analysis to predict the prognosis of patients with oesophageal carcinoma[1] using 15 discrete variables concerning each of 123 patients with oesophageal carcinoma. We identified three discrete variables (resectability, DNA distribution pattern[6] and postoperative complication), as pertinent prognostic factors. The survival rates for patients were then determined, based on all possible combinations of these three prognostic factors. We examined these three prognostic factors and explored whether the prognosis could be improved and whether there is a reliable factor which can be used to estimate the prognosis after surgery.

Patients and methods

Patients

One hundred and twenty-six Japanese patients with oesophageal carcinoma underwent oesophagectomy and oesophageal reconstruction in the Department of Surgery II, Kyushu University Hospital, from 1971 to 1984. Among these 126, 3 patients died of other causes during the follow-up period (2 of heart failure with myocardial infarction, 1 of pneumonia), as confirmed by autopsy. These three were excluded from this study However, three others who died within 1 month of surgery were included. The remaining 123 all had squamous cell carcinoma diagnosed by endoscopic biopsy. All patients received pre-operative therapy of 30 mg bleomycin (average) and radiotherapy of 30 Gy X-ray (average), and were followed clinically for at least 2 years postoperatively Macroscopic and microscopic evaluations were made according to rules established by the Japanese Society of Oesophageal Diseases[7]. The DNA distribution pattern was not determined in those who were not surgically treated.

After the application of multivariate analysis to the 15 prognostic variables listed in *Table 1*, we found that only 3, resectability of the carcinoma, DNA pattern of the cancer cells[6] and postoperative complications, correlated with prognosis with a statistical significance ($P<0{\cdot}05$). Each of these three variables was assigned either a 'favourable' (+) or 'unfavourable' (−) prognostic factor. Therefore, we subdivided the patients into four groups, according to the combination of favourable and unfavourable variables (*Table 2*)

After univariate analysis of the 15 prognostic variables, the best model was examined by both the forward and backward step method, in a step-wise model.

Analysis of DNA content in cancer cells

Cellular DNA analysis of the biopsy specimens of oesophageal carcinoma from patients given no radiation or chemotherapy before the biopsy was performed on paraffin sections cut at 10 μm, stained with Feulgen, and examined by the two wave-length method[8] In each section, 100 cancer cells were measured. The histogram of DNA content was determined by comparing the DNA content of each cancer cell to the mean value of 25 lymphocytes, used as the control. As shown in *Figure 1*, the distribution of DNA content was grouped into four types according to ploidy and dispersion[6]. In our study, types I and II were designated as favourable DNA patterns and types III and IV as unfavourable

Statistical analysis

Survival rates were estimated using the method of Kaplan and Meier[9], and the significance was determined using a generalized Wilcoxon test[10] In addition, the multiple regression procedure proposed by Cox[5] was applied in a multifactorial analysis of prognostic factors for the 123 patients Significance analyses were performed using a χ^2 test to compare the following 15 variables (*Table 1*): age, sex, site of carcinoma, length of tumour, pathological invasion to the adventitia, microscopic lymph node metastasis, lymphatic invasion, vascular invasion, intra-epithelial spread, infiltration (INF), DNA pattern, histological type, histological stage, resectability in surgery and postoperative complication. Three types[7] of infiltration were identified, INF-α characterized by an expansive growth pattern, INF-γ characterized by an infiltrative growth pattern, and INF-β intermediate between INF-α and INF-γ.

Results

Univariate and multivariate analysis

Table 1 summarizes the multivariate analyses of 15 variables. Of these variables, the ones with a statistical significance were the DNA distribution pattern ($\chi^2=8{\cdot}46$, d.f. 2, $P=0{\cdot}02$), resectability ($\chi^2=6{\cdot}56$, d.f. 1, $P=0{\cdot}01$), and postoperative complication ($\chi^2=4{\cdot}23$, d.f. 1, $P=0{\cdot}04$).

In the univariate analysis of the 15 prognostic variables,

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Table 1 *Multivariate analysis using Cox's proportional hazards model in 123 patients with oesophageal carcinoma*

Variables	Categories	No of patients	Regression coefficients	χ^2-value (d.f.)	Probability
Age in years	30–49	8	−0·223	0·39	0·82
	50–69	85	−0·006	(2)	
	>70	30	0·078		
Sex	Male	104	0·006	0·02	0·90
	Female	19	−0·032	(1)	
Site of carcinoma	Upper	80	0·007	0·33	0·85
	Middle	13	0·133	(2)	
	Lower	30	−0·077		
Length of tumour (cm)	≤4·0	29	−0·364	4·10	0·13
	4·1–8·0	79	0·055	(2)	
	≥8·1	15	0·416		
Pathological invasion to the adventitia	No invasion	35	0·016	0·63	0·73
	Invasion positive	48	−0·096	(2)	
	Invasion to the neighbouring tissues	40	0·101		
Microscopic lymph node metastasis	None	59	−0·230	3·83	0·06
	Positive	64	0·212	(1)	
Lymphatic invasion	None	57	−0·141	1·37	0·24
	Positive	66	0·122	(1)	
Vascular invasion	None	85	−0·098	1·84	0·18
	Positive	38	0·220	(1)	
Intra-epithelial spread	None	96	0·100	2·90	0·09
	Positive	27	−0·354	(1)	
Infiltration (INF)	α	19	−0·106	5·69	0·06
	β	71	−0·158	(2)	
	γ	33	0·402		
Histological types	Poorly	25	0·223	5·22	0·07
	Moderately	65	0·113	(2)	
	Well	33	−0·392		
Histological stage	S0	11	−0·026	0·10	0·99
	S1, S2	15	−0·055	(3)	
	S3	40	0·047		
	S4	57	−0·013		
DNA distribution pattern	I, II	27	−0·663	8·46	0·02
	III	48	0·037	(2)	
	IV	48	0·336		
Resectability	Complete resection	55	−0·346	6·56	0·01
	Incomplete resection	68	0·280	(1)	
Postoperative complication	None	58	−0·236	4·23	0·04
	Positive	65	0·211	(1)	

d.f., Degrees of freedom, α, infiltration characterized by an expansive growth pattern, γ, infiltration characterized by an infiltrative growth pattern, β, a growth pattern intermediate between α and γ

Table 2 *Combination of favourable and unfavourable prognostic variables*

Groups	No of patients	Resectability	DNA pattern	Postoperative complication
1	13	(+)	(+)	(+)
2	7	(−)	(+)	(+)
	16	(+)	(−)	(+)
	4	(+)	(+)	(−)
3	22	(+)	(−)	(−)
	3	(−)	(+)	(−)
	22	(−)	(−)	(+)
4	36	(−)	(−)	(−)

(+), Favourable prognosis, (−), unfavourable prognosis.
Complete resection was a positive prognostic indicator (+) and incomplete resection was a negative one (−). Favourable DNA pattern (Type I and II) was a positive prognostic indicator (+) and unfavourable DNA pattern (type III and IV) was a negative one (−) An uneventful postoperative course served as a positive prognostic indicator (+), and an eventful postoperative course was a negative one (−)

those with a statistical significance were: length of tumour, pathological invasion into the adventitia, microscopic lymph node metastasis, lymphatic invasion, vascular invasion, INF, and histological stage, as well as DNA distribution pattern, resectability and postoperative complication.

The DNA distribution pattern had a statistical significance as a prognostic factor, when the 15 variables were examined by both forward and backward step methods However, postoperative complications and resectability had a statistical significance as a prognostic factor only by the backward step method.

The incidence and type of postoperative complications of 123 patients are summarized in *Table 3*. Pulmonary complications were the most frequent with 39 patients (31·7 per cent), and there were 3 operative deaths (2·4 per cent).

Survival rates of oesophageal carcinoma

Figure 2 shows the survival curve of all 123 patients. Survival rate decreased rapidly in the first 2 years after operation and more slowly thereafter. One-, two-, three-, four- and five-year survival rates were 55, 35, 27, 23 and 23 per cent, respectively.

*Figure 3***a** shows the percentage survival of patients with complete (55 cases) and incomplete (68 cases) resection. Three-year survival rates of patients with complete and incomplete resection were 46 and 8·3 per cent, respectively. The differences were statistically significant ($P < 0·01$), as determined by the generalized Wilcoxon test.

*Figure 3***b** shows the percentage survival of patients with favourable (27 cases) and unfavourable (96 cases) DNA distribution patterns. Three-year survival rates were 57 and

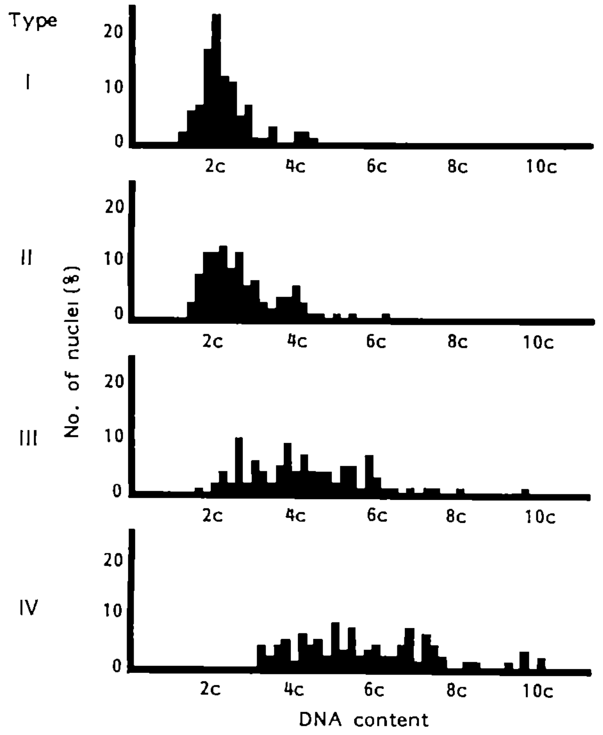

Figure 1 *Classification of DNA distribution pattern in oesophageal carcinoma Type I, a peak in the 2c region with a dispersion to the 4c region, type II, a peak in the 2c–3c regions with a dispersion limited up to the 6c region, type III, a low peak beyond the 3c region and a low proportion of cells (<20 per cent) in >6c, type IV, a high proportion of cells (>20 per cent) in >6c. In this study, there was no case of type I, 27 cases of type II, 48 cases of type III and 48 cases of type IV*

Table 3 *Postoperative complications in 123 patients*

	n (%)
Complications (total)*	65 (52·8)
Lung	39 (31·7)
Anastomotic leakage	9 (7·3)
Liver damage	5 (4·1)
Heart failure	2 (1·6)
Renal failure	1 (0·8)
Others	19 (15·4)
No complications	58 (47·2)
Operative mortality	3 (2·4)

* Eight patients had two or more complications

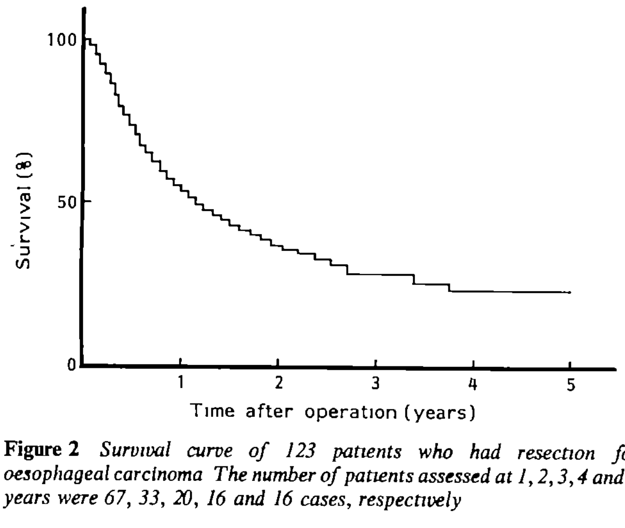

Figure 2 *Survival curve of 123 patients who had resection for oesophageal carcinoma The number of patients assessed at 1, 2, 3, 4 and 5 years were 67, 33, 20, 16 and 16 cases, respectively*

18 per cent, respectively. There was a statistical difference ($P<0{\cdot}01$), as determined by the generalized Wilcoxon test.

Figure 3c shows the survival rates of patients with no postoperative complication (58 cases) and those with at least one postoperative complication (65 cases). Three-year survival rates of patients, with and without postoperative complications, were 37 and 19 per cent, respectively There was a statistical difference ($P<0{\cdot}05$), as determined by the generalized Wilcoxon test.

Figure 4 shows the survival curves of patients with all favourable prognostic factors (group 1 included 13 patients), those with only one unfavourable prognostic factor (group 2 included 27 patients), those with only one favourable prognostic factor (group 3 included 47 patients) and those with all unfavourable prognostic factors (group 4 included 36 patients).

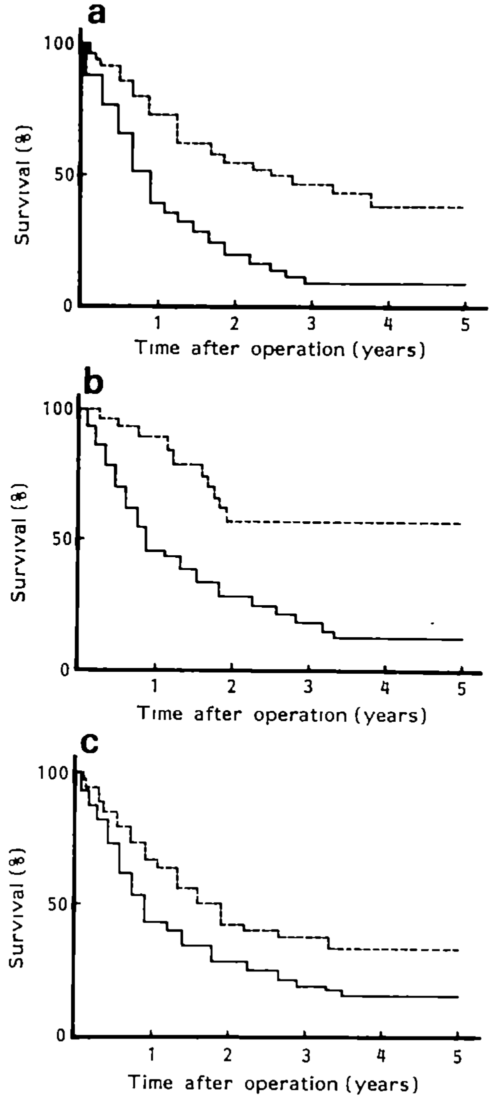

Figure 3 *Survival curves of patients, based on each prognostic factor* **a**, *Survival curve of patients with complete (– – –) and incomplete (——) resection The numbers of patients with complete resection assessed at 1, 2, 3, 4 and 5 years were 40, 25, 18, 14 and 14, respectively Those with incomplete resection at 1, 2, 3, 4 and 5 years numbered 27, 8, 2, 2 and 2 cases, respectively* **b** *Survival curve of patients with favourable (– – –) and unfavourable (——) DNA distribution patterns. The numbers of patients with favourable DNA patterns assessed at 1, 2, 3, 4 and 5 years were 24, 12, 10, 10 and 10, respectively Those with an unfavourable DNA pattern at 1, 2, 3, 4 and 5 years numbered 43, 21, 10, 6 and 6, respectively* **c**, *Survival curve of patients with no postoperative complication (– – –) and those with at least one postoperative complication (——). The numbers of patients without postoperative complications, as assessed at 1, 2, 3, 4 and 5 years were 39, 18, 10, 8 and 8, respectively Those with postoperative complications numbered 28, 15, 10, 8 and 8, respectively*

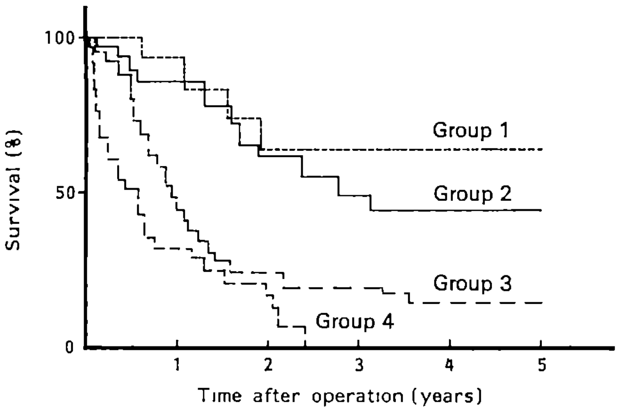

Figure 4 *Survival curves of patients with positive or negative prognostic factors. Group 1* (n = *13*), *patients with positive prognostic factors* (*the numbers of patients assessed at 1, 2, 3, 4 and 5 years were 12, 6, 5, 5 and 5, respectively*), *group 2* (n = *27*), *patients with only one negative prognostic factor* (*the numbers of patients assessed at 1, 2, 3, 4 and 5 years were 23, 13, 8, 6 and 6, respectively*), *group 3* (n = *47*), *patients with only one positive prognostic factor* (*the numbers of patients assessed at 1, 2, 3, 4 and 5 years were 20, 8, 7, 5 and 5, respectively*); *group 4* (n = *36*), *patients with negative prognostic factors* (*the numbers of patients assessed at 1, 2 and 3 years were 11, 4 and 0, respectively*)

Statistically significant differences were found between groups 1 and 3 ($P<0{\cdot}001$), groups 2 and 3 ($P<0{\cdot}001$), and groups 3 and 4 ($P<0{\cdot}01$), though not between groups 1 and 2, as determined by the generalized Wilcoxon test.

Discussion

The histological finding of lymph node metastasis and the presence of vascular or lymphatic permeation by cancer cells have been widely accepted as unfavourable prognostic factors in patients with a malignancy[11]. However, for carcinoma of the oesophagus, it is difficult to predict the exact prognosis in each patient because there are so many inter-related factors. This report has shown that, in individual cases, the conventional histopathological study yields little information concerning the prognosis. Using a multivariate analysis, three of fifteen variables proved to be important prognostic factors. The DNA distribution pattern proved to be one of the most reliable factors correlated with prognosis of the patients after oesophagectomy.

The cytophotometric DNA pattern of the biopsy specimens in all patients with oesophageal carcinoma[6,8] was one of the most important prognostic factors. These measurements of DNA content clearly defined the malignant potential. Thus, the stage of differentiation of the oesophageal carcinoma varies with each patient, even in minute carcinomas. A favourable DNA pattern was the most important prognostic indicator.

The occurrence of postoperative complication was also an important prognostic factor. Complications are apparently influenced by the physical status of the patients[3,4], operative indicators[12], operative procedures[13], and postoperative management[14]

Our data indicate that patients possessing two or more favourable prognostic indicators had a comparatively high survival rate, that is, over 60 and 40 per cent were noted in these groups at 2 and 5 years after surgery, respectively. On the other hand, patients with two or more unfavourable prognostic indicators did poorly and, in particular, all those with all three negative indicators died within 3 years of surgery.

Of these three prognostic indicators only the DNA pattern appears to be independent of medical intervention. As the resectability completely depends on early detection, every effort should clearly be made to detect the oesophageal carcinoma at an early stage As one of the diagnostic investigations of oesophageal carcinoma, endoscopic ultrasonography is accurate in detecting the extent of infiltration of the tumours and adjacent lymph node involvement[15], while computed tomography will reveal distant metastases[16]. These examinations will aid in determining appropriate operative procedures. To avoid complications, meticulous pre- and postoperative care has to be provided for all patients undergoing oesophageal surgery.

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Surgical treatment of acute necrotizing pancreatitis

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Between January 1980 and June 1986, 21 patients required surgery for acute necrotizing pancreatitis. Four patients had been transferred from other hospitals; the remaining 17 patients had been treated from the outset at Glasgow Royal Infirmary, representing 3·7 per cent of the 456 patients treated for acute pancreatitis during this time. Necrosectomy was performed on 14 patients and 7 patients were treated by pancreatic resection, with 4 deaths in each group; thus 8 patients (38 per cent) died at a median time of 22 days from onset of their attack. Three of the four patients transferred to our care died, giving a mortality in our own patients of 29 per cent. Of the survivors, all but three had a prolonged and complicated hospital course. Our data confirm that acute necrotizing pancreatitis is still associated with a considerable mortality and morbidity. Early multi-organ failure, advanced age, underlying medical illness and the presence of infected necrosis were associated with a poor outcome. Necrosectomy delayed until the second or subsequent week appeared to be a suitable procedure for the majority of our patients, but shortcomings were apparent with the traditional methods of closed drainage of the pancreatic bed postoperatively. The many demands imposed by this small group of patients suggests that their management is best undertaken in centres in which there is special expertise and this should contribute to a further reduction in the mortality from this condition.

Keywords: Acute necrotizing pancreatitis, operation

Acute pancreatitis in the majority of patients (75–80 per cent) is a mild, self-limiting illness with a mortality rate of < 3 per cent[1]. A small proportion of patients will develop a severe illness, acute necrotizing pancreatitis, which in the past has been attended by a high mortality when treated by conventional supportive measures alone. The role of surgery in the management of acute necrotizing pancreatitis is no longer in dispute although the need to remove uninfected necrosis is debated. Controversy also exists regarding the ideal timing of surgery (early or late) and the type of procedure performed (pancreatic resection or necrosectomy) Furthermore, the lack of an agreed terminology for the various local complications of pancreatitis and the procedures performed presents difficulties when comparing results from different centres.

Patients and methods

Between January 1980 and June 1986, 456 patients were treated for acute pancreatitis in the surgical wards of Glasgow Royal Infirmary. Twenty-one of these patients have required surgery for acute nectrotizing pancreatitis Our definition of acute necrotizing pancreatitis encompasses patients with necrotic pancreatic or, more often, peripancreatic tissue and includes patients who, when operated on at a later stage, have pus as an additional feature. This definition excludes patients with pseudocyst or localized pancreatic abscess without necrosis who are considered to have a better prognosis. Of the 21 patients with acute necrotizing pancreatitis, 17 (81 per cent) had presented directly to the medical and surgical wards of this hospital and represent 3·7 per cent of the 456 patients with acute pancreatitis treated during this time Four patients had been referred from other hospitals Details of the patients' age and sex and of the aetiologies of the attacks are given in *Table 1* During this period another 20 patients required non-elective surgery for other complications of acute pancreatitis, none of whom was considered to have necrotizing pancreatitis

Diagnosis

Acute pancreatitis was first diagnosed at laparotomy in 4 (19 per cent) of the 21 patients with acute necrotizing pancreatitis Of these 4 patients, 3 had a serum amylase determination made on admission with values of 326, 379 and 496 units/l respectively (normal range 70–300 units/l). Two had first presented to physicians, being referred to our care 5 and 17 days post-admission. One further patient had presented to the obstetricians, having developed acute pancreatitis in the 35th week of her pregnancy In the remaining 17 patients the diagnosis of acute pancreatitis was initially made on the basis of an elevated serum amylase with a consistent clinical presentation[2] Two of these patients had amylase levels just below the 'diagnostic level' of 1200 units/l with values of

Table 1 *Aetiology, age and sex distribution in patients with acute necrotizing pancreatitis and incidence of each aetiology as a proportion of all attacks of pancreatitis treated*

Aetiology	*n* (%)	M : F	Mean age (range)	Aetiology as percentage of all attacks*
Alcohol	9 (43)	9 : 0	42 (32–49)	34
Gallstone	6 (29)	3 : 3	48 (22–69)	34
Idiopathic	3 (14)	2 : 1	66 (57–70)	22
Postoperative	3 (14)	0 : 3	62 (55–66)	3
Total	21	14 : 7	50 (22–70)	

* All attacks recorded during the period of study

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Table 2 *Indications for surgery clinical factors and results of laboratory and radiological investigation*

	Operative findings		
	Peripancreatic necrosis		Pancreatic parenchymal necrosis ($n=9$)
Indications	Localized ($n=2$)	Extensive ($n=10$)	
Clinical factors			
Pyrexia/leucocytosis	1	7	2
Deteriorating condition	0	2	7
'Failure to improve'	1	1	0
Body wall ecchymosis	0	2	2
Abdominal mass	0	5	4
Multi-organ failure	0	1	3
Prognostic tests			
Mean prognostic factor score*	1	3·6	4
Haemorrhagic peritoneal fluid†	0	2/3	6/7
Ultrasound			
Fluid collection	1	3	2
Necrosis	0	1	1
Not seen/not diagnostic	0	3	2
Computed tomography			
Necrosis	1	3	1

* Glasgow multiple factor scoring system (Reference 3); † haemorrhagic fluid at paracentesis or laparotomy and thus meeting the Leed's criteria for severe acute pancreatitis (Reference 4)

Table 3 *Initial surgical procedure, delay to surgery and outcome*

Initial procedure	No. of patients	Delay to surgery*	Death	Alive/major complication	Alive/no complication
Resection	7	7 (1–122)	4	3	—
Necrosectomy	14	23 (3–150)	4	7	3
Total	21	21 (1–150)	8	10	3

* Days, median (range)

1100 and 1130 units/l respectively but both had urinary amylase levels that were considered diagnostic

Treatment

Initial therapy consisted of intravenous fluids, nasogastric suction, analgesia with pethidine, bladder catheterization and hourly monitoring of the urine volumes. Arterial blood gas analysis was performed regularly and oxygen provided by mask if the P_{O_2} fell below 70 mmHg. Antibiotics, H_2 receptor antagonists and fresh frozen plasma were not routinely administered. Prognostic scoring factors[3] were collated, 16 patients (76 per cent) having severe disease predicted. Of the five patients not meeting the criteria for severe acute pancreatitis three had incomplete documentation of their prognostic factors.

Additional therapy before surgery included peritoneal lavage in three patients One was lavaged for 30 hours after diagnostic laparotomy with apparent symptomatic benefit Lavage was without benefit in two others with multi-organ failure and a rapidly deteriorating clinical course.

Indications for surgery

The decision to undertake surgery was made primarily on clinical grounds, coupled with information from diagnostic imaging in 10 patients (*Table 2*) Persistent fever and/or leucocytosis, usually despite a trial of antibiotics but associated with a relatively stable clinical course, was the main clinical indication for surgery in 10 patients (48 per cent) A deteriorating clinical condition, despite full supportive therapy, was the main indication for surgery in nine patients (43 per cent) and this includes four with multi-organ failure and two with overt and suspected intra-abdominal bleeding 'Failure to improve' was the indication for surgery in two patients who had been demonstrated on diagnostic imaging to have evidence of pancreatic necrosis and a peripancreatic fluid collection, respectively.

Surgery

Surgery was performed through a high transverse or 'roof-top' incision and after full laparotomy the pancreas was exposed by division of the gastrocolic omentum. Necrosis limited to the body and/or tail of the pancreas was dealt with by formal distal resection Subtotal resection or necrosectomy (digital débridement of non-viable pancreatic and peripancreatic tissue) was performed for more extensive necrosis Necrosis involving the head of the gland or predominently superficial/peripancreatic necrosis was treated by necrosectomy In all but one case the abdominal wound was closed primarily with simple drainage or sump drainage of the pancreatic bed. In one patient, because of persistent bleeding from the pancreatic bed, the wound was partially closed and the splenic bed packed with large gauze surgical packs (25 x 25 cm).

Histology of the resected pancreatic specimens showed peripancreatic necrosis and parenchymal necrosis of variable extent. Histology of tissue débrided at necrosectomy confirmed necrotic tissue and debris This was considered to represent necrotic peripancreatic tissue where the underlying pancreas appeared reasonably preserved at operation. The histological extent of any pancreatic parenchymal necrosis in the remaining gland in such cases is, of course, unknown. The patients have been studied according to whether the necrosis involved the pancreatic parenchyma (confirmed histologically on the resected specimens or on operative findings), or whether the necrosis appeared to be mainly of the peripancreatic tissues, based on the findings at necrosectomy This latter group of patients was further subdivided according to whether the peripancreatic necrosis was confined to one area, usually the head of the pancreas, or was extensive. Swabs and samples of fluid and tissue were routinely cultured for bacteriology

Statistics

Statistical analysis was performed using the χ^2 test with Yates' correction and the Mann–Whitney U test

Results

Surgery

Table 3 details the initial surgical procedures performed, the delay to surgery and the outcome. A total of 7 patients underwent a formal pancreatic resection (distal, 5; subtotal, 2)

Table 4 *Major complications after surgery in each group*

Complications	Resection ($n=7$)	Necrosectomy ($n=14$)
Local		
Abscess/necrosis	2	6
Fistula pancreatic	1	3
small bowel	1	—
colon	1	1
Bleeding	3	1
Splenic venous thrombosis	—	1
Duodenal obstruction	—	2
Biliary obstruction	1	—
Systemic		
Respiratory failure*†	7	5
Renal failure*	3	2
Diabetes	1	1

* Includes 4 patients with pre-operative multi-organ failure; † requiring mechanical ventilation for > 24 h after surgery

with 4 deaths. Four of the resections were performed within the first week of illness. Two of these patients came to resection within the first 30 h because of fulminant pancreatitis unresponsive to intensive therapy including peritoneal lavage. Both patients had extensive pancreatic parenchymal necrosis at laparotomy and this was complicated in one by massive infarction of the small bowel and colon due to splenic and superior mesenteric venous thrombosis. Neither responded to surgical treatment, both dying within 12 h of surgery. Another patient with early multi-organ failure also died after delayed pancreatic resection on day 19 for retroperitoneal bleeding. One further patient died following resection on day 122 for pancreatic necrosis complicated by sepsis and bleeding, having originally undergone pseudocyst drainage by cystogastrostomy on day 93.

Fourteen patients underwent primary necrosectomy, with four deaths. One patient who died had developed early multi-organ failure after diagnostic laparotomy in another hospital. His condition failed to improve following necrosectomy on day 14 and he died 2 days later. Three of the patients undergoing necrosectomy had associated fluid collections but in only one was a formal drainage procedure undertaken concurrently (cystoduodenostomy). Two others had earlier undergone pseudocyst drainage by cystogastrostomy on day 19 and day 90. Both had evidence of pancreatic necrosis associated with sepsis before necrosectomy was performed on day 51 and 150, respectively.

Additional procedures performed at the first operation included cholecystectomy in seven patients, two of whom had common duct exploration. Gallstones were recovered in six of these patients. Cholecystostomy was performed in two patients because of the presence of a tense, dilated gallbladder at laparotomy. Two others underwent transverse colectomy and one a subtotal small and large bowel resection (mentioned above) because of ischaemia. A gastrojejunostomy was performed in one patient for gastric outlet obstruction and six (five having necrosectomy) had a feeding jejunostomy established.

Complications

Major complications were frequent and are detailed in *Table 4*. All three survivors following pancreatic resection had a prolonged postoperative course, finally being discharged between 4 and 16 months (median 135 days) after admission. Eleven of the patients undergoing necrosectomy had a complicated postoperative course, the survivors finally being discharged between 2 and 9 months (median 85 days) from the onset of their attack.

Of the total group, 11 patients (52 per cent) required further operative procedures which are detailed in *Table 5*.

Outcome

Eight patients (38 per cent) died at a median time of 22 days from onset of the attack (range 2–140 days) Of the 4 patients transferred to our care, 3 died, giving a mortality of 29 per cent for the 17 patients treated by us from the outset. Five of these eight patients died within 4 days of their first operation. Sepsis and/or multi-organ failure was the major cause of death in six patients, sepsis accounting for three of the four deaths following necrosectomy. Haemorrhage was the major cause of death in the other two patients. Mortality was not found to be related to the timing of the surgical intervention Five patients had intervention within the first week (four by resection), with two deaths. Five were operated on during the second week, with one death, six were operated on at between 2 weeks and 1 month, with three deaths; and five were operated on after 1 month, with two deaths. None of the patients with localized peripancreatic necrosis died, compared with three of the ten with extensive peripancreatic necrosis and five of the nine with pancreatic parenchymal necrosis.

No deaths were recorded in the three patients with postoperative pancreatitis whereas 33 per cent of those with gallstone or alcohol-associated pancreatitis died. Those patients with idiopathic pancreatitis were older, with a mean age of 66 years and all three died. The mean age of the patients who died was 53 years compared with 48 years for the survivors. Of the 8 patients who died, 6 had significant pre-existing medical conditions, compared with only 3 of the 13 survivors but neither this difference nor the age difference was statistically significant. The mean prognostic factor score did not distinguish the two groups (survivors 3·9, non-survivors 3·4) but all four patients with early multi-organ failure and requiring mechanical ventilation pre-operatively died. All four of the patients with body wall staining survived. Of the 14 patients with infected necrosis, 7 (50 per cent) died compared with only one of the 7 (14 per cent) without infection. From the larger group of 14 patients, 5 had infected necrosis present at their first operation (3 within the first week of illness), and 4 of these patients died Infected necrosis was found at the first pancreatic procedure in two patients who had undergone an earlier diagnostic laparotomy and in one following elective biliary surgery. In the remaining six patients infected necrosis was recovered at the second or subsequent pancreatic procedure. Of the five patients found to have infection at the first operation, two had received no antibiotics and one had received a single dose of ampicillin pre-operatively The two other patients had received a course of either gentamicin or cephaloridine and at operation were found to have infection with anaerobic organisms and coliforms respectively. Of those found to have sterile necrosis at their first operation, half had received broad-spectrum antibiotics, usually in combination with metronidazole. Courses of antibiotics were

Table 5 *Subsequent surgical procedures in each group*

Procedure	Resection 5 (71%)	Necrosectomy 6 (43%)
Drain abscess	2	4
Necrosectomy	1	5
Pancreatic resection	—	2
Cholecystectomy	—	1
Colectomy	—	1
Colostomy	1	—
Small bowel operations	6	1
Feeding jejunostomy	—	1
Splenectomy	—	3
Biliary bypass	2	—
Gastrojejunostomy	—	1
Repair aortoduodenal fistula	2	—
Arrest bleeding	4	—
Total reoperations	16	13
Reoperations/patient	1–7	1–4

not associated with freedom from infection at the second or subsequent operations.

Discussion

The optimal surgical management of acute necrotizing pancreatitis remains controversial. Reviewing the collective experience from 12 European centres Hollender *et al.* found an average mortality rate of 42 per cent for sub-total pancreatectomy and 60 per cent for total pancreatectomy[5]. Two recent studies recommending resection have reported mortality rates of 33 per cent[6] and 22 per cent[7], the results in the latter study from Finland[7] being achieved in a predominantly young, male, alcoholic patient population with a mean age of 37 years. However, another group from Finland has sounded a distinct note of caution about resection, citing the difficulties of determining the extent of pancreatic necrosis at laparotomy and the not inconsiderable longer-term morbidity encountered[8–10].

The more conservative approach of delaying surgery until the second or subsequent weeks and removing only non-viable pancreatic and peripancreatic tissue (necrosectomy) appears to be becoming increasingly popular and has been the aim of our approach to this problem Hollender *et al.* reported an overall mortality of 37 per cent for necrosectomy from the 12 centres cited[5], a figure little different from that for subtotal resection or for our own patients Beger *et al.* in 1985 reported a 24·4 per cent mortality in 205 patients predominantly managed by necrosectomy[11] and more recently have attained a mortality of 8·3 per cent in 61 patients treated by necrosectomy and postoperative lavage of the lesser sac, lavage in these patients being continued for a median time of 21 days[12]. Similar success has been reported by others: Bradley and Fulenwider achieved a 14 per cent mortality in a smaller group of 21 patients treated by necrosectomy and open packing of the lesser sac[13]. Others have questioned the place of necrosectomy, considering it to have only a limited application[14].

The decision to undertake surgery and the timing of surgery in our patients was based on clinical judgement, although information from diagnostic imaging contributed to this decision in 10 patients. Precise indications for surgery have been difficult to establish. Improved CT scanning, particularly with the advent of contrast-enhanced scanning, may be helpful in this context, appearing to be able to differentiate viable (enhancing) from non-viable pancreatic tissue[15]. Given the reported difficulties in determining the extent of pancreatic necrosis at laparotomy[8], this information should prove of great value to the surgeon planning the necrosectomy. However, the demonstration of non-enhancing pancreatic tissue alone may not in itself be a definite indication for surgery. Our own data and that of Beger's group[16] indicate that the presence of infected necrotic tissue is associated with a poorer prognosis. Delaying surgery in the presence of infected pancreatic necrosis until clinical deterioration occurred was considered to be a factor in two patients who died in the early part of the series Imaging guided fine-needle aspiration of this tissue for bacteriological examination[17] may provide a stronger indication for surgery if infection is demonstrated, whereas the finding of sterile necrosis might allow a 'wait and see' policy should the patient's condition permit.

Although the majority of patients with acute necrotizing pancreatitis can be managed by this delayed approach, a minority who present with fulminant acute pancreatitis may continue to deteriorate despite full intensive care and even peritoneal lavage. Early operation with pancreatic resection offers the only chance of salvaging such patients. Both patients in our series falling into this category died and in each case surgery within 30 h of admission was probably too late. Contrast-enhanced CT scanning may prove useful for the earlier identification of such cases[15]

In patients surviving the early phase of their illness the actual pancreatic procedure performed will depend on the laparotomy findings and particularly on the extent and site of the necrosis. Judging from the data of Hollender *et al.*[5] there may in fact be little to choose between necrosectomy and resection The results of our series suggest that those undergoing resection have a more prolonged, complicated postoperative course but fewer problems with sepsis and recurrent necrosis than those undergoing necrosectomy. However, the small numbers involved and the differing indications and timings of surgery in the two groups prevents any realistic comparison. According to Nordback and co-workers, histological examination of pancreatic specimens which had been formally resected for acute necrotizing pancreatitis often showed the presence of extensive peripancreatic necrosis but only limited parenchymal necrosis, eight of their patients showing no parenchymal necrosis whatsoever[8,9]. This would be in keeping with our own findings and clearly a formal pancreatic resection for 'pancreatic necrosis' in this situation often overtreats the underlying pathology. If it is possible, it seems sensible to conserve all viable pancreatic tissue by the technique of necrosectomy.

The techniques of postoperative lesser sac lavage and open packing are both said to deal successfully with continuing infection and/or necrosis in the remaining pancreas after necrosectomy. Sepsis and necrosis had been a problem in six (43 per cent) of our patients treated initially by necrosectomy and closed drainage, ultimately leading to death in three of them. The three survivors each had a prolonged postoperative course requiring respectively one, three and four reoperations. Closed drainage postoperatively was, however, successful in seven patients. Necrosis in these seven patients was more often peripancreatic and/or localized and only one had infected necrotic tissue at the time of the first pancreatic procedure compared with three of the four who died. Patients found to have either extensive or infected necrotic tissue at operation appear to be at high risk and may be considered for postoperative lesser sac lavage or open packing.

The majority of patients with pseudocysts consequent on acute pancreatitis settle following internal drainage. However, in a few cases the inflammation fails to subside, perhaps because of unsuspected parenchymal necrosis. This was considered as an explanation for the deterioration in the two patients initially treated by delayed cystogastrostomy. Necrotic tissue (presumably peripancreatic tissue) is often found in the base of a pseudocyst and it is now our policy to remove this gently at the time of operation although it is not clear whether this decreases the risk of later complications. The third patient treated by cystogastrostomy on day 19 might have been better served by necrosectomy at the initial procedure.

With only 21 patients treated for this condition by 4 different surgeons over the period of our study, it is difficult for any one individual to gain expertise in the management of these patients and their complex problems. Management of these patients by one or two surgeons in specialist referral centres should be advantageous and a factor in reducing the mortality of this complication. Although these extremely ill patients are demanding in terms of nursing, intensive care and surgical input, acute necrotizing pancreatitis is in relative terms a small problem, accounting for only 3·7 per cent of the 456 patients treated for acute pancreatitis in our hospital during the study period. The eight deaths reported here represent only 19 per cent of the total number of deaths from acute pancreatitis recorded prospectively. Furthermore, if those patients transferred to our care are excluded, the remaining deaths represent only 13·5 per cent of the pancreatitis deaths in our own practice. Clearly, improvements in treatment of this small sub-group of patients will not have a dramatic effect on the mortality rate of 9 per cent for those cases of acute pancreatitis diagnosed in life, a rate which has remained essentially unchanged since 1974, and will have even less effect if the overall mortality rate (including cases first diagnosed at post-mortem examination) is considered[18].

Our data show that acute necrotizing pancreatitis is still associated with a considerable mortality and morbidity. Early multi-organ failure, advanced age, underlying medical illness and the presence of infected necrotic tissue are all associated with a poor outcome. Necrosectomy delayed until the second or subsequent week is a suitable procedure for the majority of patients with acute necrotizing pancreatitis. However, our results indicate the shortcomings that may be associated with the traditional approach of closed drainage of the pancreatic bed. More recently we have adopted the technique of open packing of the pancreatic bed after necrosectomy but we have not yet discerned any clear benefit in terms of survival and retain an open mind as to the ultimate role of this approach or the alternative approach of postoperative lesser sac lavage[11].

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Hepatocellular pseudotumour (regenerating nodule) in the cirrhotic liver mimicking hepatocellular carcinoma

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During a recent 6-year period we have encountered 10 patients with 'hepatocellular pseudotumour in the cirrhotic liver' (regenerating hyperplastic nodule). The patients were all male, aged 40–82 years. Seven were chronic alcohol consumers. None was positive for HBs-Ag but seven had either anti-HBs or anti-HBc. Serum AFP level ranged from 4 to 28 ng/ml in six patients who did not have hepatocellular carcinoma at the time of the diagnosis of the pseudotumour. The lesions were depicted by ultrasonography in seven, by computed tomography in two, and by angiography in one case. Liver scan was negative in all five cases investigated. The pre-operative diagnosis was definitely or highly suspicious of hepatocellular carcinoma in three, of pseudotumour in the cirrhotic liver in three, and of recurrent carcinoma in one. In another three patients, pseudotumour was coincidentally discovered in resected specimens with hepatocellular carcinoma. The histopathological and follow-up studies demonstrated synchronous or metachronous development of carcinoma in seven patients. Whether or not these lesions in the cirrhotic liver are premalignant remains to be elucidated.

Keywords: Hepatocellular carcinoma, pseudotumour, cirrhosis

The strong link between hepatocellular carcinoma (HCC) and liver cirrhosis is well recognized, and many physicians attempt early detection of HCC nodules by close follow-up of cirrhotic patients[1–3]. The most useful tool for this purpose may be a combination of serial determination of serum α-fetoprotein levels and periodic ultrasonography, both of which are non-invasive.

We have recently reported three patients with a regenerating hyperplastic nodule in the cirrhotic liver which clinically mimicked HCC, and termed such lesions 'hepatocellular pseudotumours in the cirrhotic liver'[4]. A fourth patient with a similar lesion was encountered thereafter. Histopathologically, most of the lesion had the same appearance seen in the previous cases, but a very tiny HCC was found in the regenerating nodule. This may be the first case of malignant transformation of a regenerating hyperplastic nodule in the cirrhotic liver. We have since encountered another six patients with similar lesions The clinicopathological features and follow-up study of the ten patients described above has shown that hepatocellular pseudotumour in the cirrhotic liver may have been related to the development of hepatocellular carcinoma in seven of them.

Patients and methods

During the past six years, hepatocellular pseudotumour in the cirrhotic liver[4] has been encountered and resected in ten patients. During the same period, 113 patients with both hepatocellular carcinoma and liver cirrhosis underwent partial hepatic resection in our unit. The ten patients were all male, aged from 40 to 82 years (mean ± s.d., 52·6 ± 11 8 years) All but one were known to have had liver disease for 6–25 years before the current admission. No patient had a history of blood transfusion but seven were chronic alcohol consumers All patients had associated liver cirrhosis which was histologically diagnosed according to the criteria of Anthony *et al*[5]. Six had minimal oesophageal varices and two had cholelithiasis (*Table 1*).

Hepatitis B markers and serum α-fetoprotein (AFP) were measured by radioimmunoassay Liver scanning with ^{99m}Tc was performed in five patients Ultrasonography, computed tomography, and selective angiography were carried out in all patients before laparotomy

Pre-operative diagnosis

Hepatocellular carcinoma was strongly suspected in the first three patients (Cases 1, 2, and 3). The pre-operative diagnosis was hepatocellular pseudotumour in the cirrhotic liver (regenerating nodule) in three patients (Cases 4, 8, and 10) In another three (Cases 5, 6, and 7), a hepatocellular pseudotumour was coincidentally discovered in resected specimens with hepatocellular carcinoma Recurrent hepatocellular carcinoma was the diagnosis in one instance (Case 9)

Operative methods

The lesions were removed by subsegmental resection of the liver in eight patients and by postero-inferior segmentectomy in one patient. Partial wedge resection was done merely for biopsy in one patient (Case 7) with multiple hepatocellular carcinomas and the hepatic artery was cannulated for later chemotherapy Cholecystectomy was performed simultaneously in the two patients with cholelithiasis. In the six patients with oesophageal varices, only ligation of the coronary vein was performed because of the minimal extent of the varices.

Follow-up of patients

All patients were followed closely in the postoperative period. Liver functions and serum AFP level were estimated at least once a month Ultrasonographic examinations were repeated every 3 months and CT scanning and angiography were performed if and when necessary.

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Table 1 *Clinical data of 10 male patients with hepatocellular pseudotumour*

Case no.	Age	Duration of liver disease (years)	Alcohol* abuse	Hepatitis B virus HBs-Ag	anti-HBs	anti-HBc	Serum AFP (ng/ml)	Other disease	Outcome
1	45	6	Yes	−	+	+	14	Oesophageal varices Cholelithiasis	41 months, died of HCC**
2	57	10	Yes	−	+	+	28	None	43 months, alive with HCC
3	41	6	Yes	−	+	+	4	Oesophageal varices	42 months, free of disease
4	40	7	No	−	−	+	42	None	27 months, free of disease
5	60	21	Yes	−	+	+	180	Oesophageal varices Diabetes mellitus	39 days, died of liver failure
6	44	18	Yes	−	−	−	314	Oesophageal varices Diabetes mellitus	12 months, died of HCC
7	82	25	No	−	−	−	14	Cholelithiasis	4 months, died of pneumonia
8	50	10	Yes	−	−	+	4	Oesophageal varices	18 months, free of disease
9	51	11	No	−	−	+	11	Oesophageal varices	12 months, free of disease
10	56	Unknown	Yes	−	−	−	14	Cholecystectomized 24 years ago	10 months, free of disease

* Those who consume more than 50 g alcohol every day for more than 5 years; **hepatocellular carcinoma

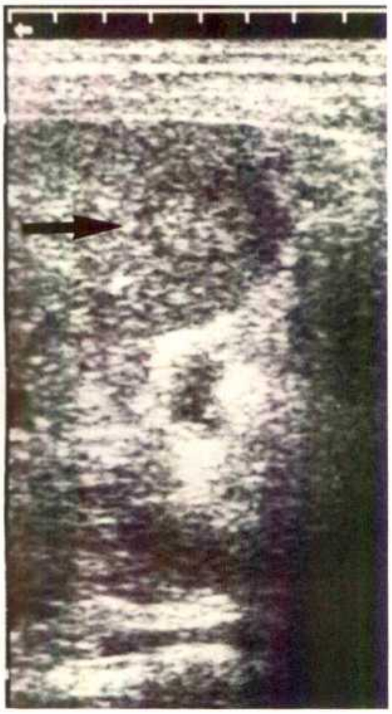


Figure 1 *Pre-operative ultrasonograms in Case 4. An isoechoic mass with hypoechoic rim as large as 3·0 × 2·8 cm was found at the anterior edge of the right hepatic lobe. There was neither lateral acoustic shadow nor enhancement of posterior echo*

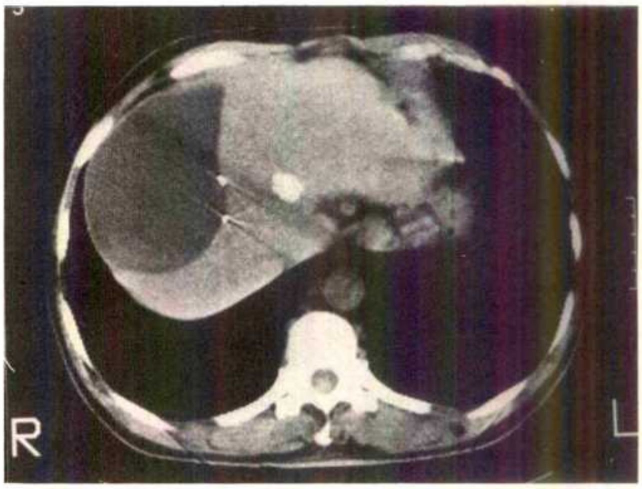


Figure 2 *Pre-operative computed tomography in Case 9. The lesion was not depicted by plain CT or CT with contrast media but was visualized by preceding intra-arterial infusion of Lipiodol. This case indicates that accumulation of lipiodol does not necessarily mean the presence of hepatocellular carcinoma in the cirrhotic liver*

Results

Hepatitis B virus

No patient was positive for HBs-antigen but seven had either anti-HBs or anti-HBc, or both. Only three patients had no evidence of hepatitis B virus infection (*Table 1*).

Serum AFP

Serum AFP levels (normal range; less than 20 ng/ml) ranged from 4 to 28 ng/ml in six patients who did not have hepatocellular carcinoma at the time of the diagnosis of hepatocellular pseudotumour. Serum AFP levels were 14–314 ng/ml in four patients who simultaneously had both hepatocellular pseudotumour and carcinoma (*Table 1*).

Radiological data

Liver scintigraphy did not demonstrate the pseudotumour in any of the five cases studied. Pre-operative ultrasonography revealed the lesion in seven patients. It was depicted as a hypoechoic mass in two, a hyperechoic mass in three, and an isoechoic mass with hypoechoic rim in two instances (*Figure 1*). Computed tomography demonstrated the lesion in only two cases, and it was enhanced with contrast media in one of them. The lesion was visualized on CT only by a preceding infusion of Lipiodol (Kodama Pharmacologic Company, Japan) in Case 9 (*Figure 2*). Angiography detected the hepatocellular pseudotumour only in one patient. In the three patients (Cases 5, 6, and 7) in whom the pseudotumour was discovered during or after operation, retrospective evaluation did not show the lesion at ultrasonography, CT or angiography. The size of the lesion in these three cases was <2 cm in diameter (*Tables 2* and *3*).

Histological findings

The relationship between hepatocellular carcinoma and pseudotumour is illustrated in *Table 3*. In two patients carcinoma occurred late after removal of a pseudotumour. Pseudotumours developed 13 months after resection of carcinomas in one instance (Case 9). Both lesions were simultaneously found in four patients, in one of whom (Case 4) a very tiny carcinoma

Table 2 *Radiological data of 10 patients with hepatocellular pseudotumour*

Case no.	Liver scan	Ultrasonography	Computed tomography	Arteriography
1	Negative	Hypoechoic mass	Negative	Negative
2	Not done	Hyperechoic mass with halo	Mass of low density, no enhancement	Tumour stain with radiolucent rim
3	Negative	Hypoechoic mass	Negative	Negative
4	Negative	Isoechoic mass with wide hypoechoic rim	Negative	Negative
5	Not done	Negative	Negative	Negative
6	Not done	Negative	Negative	Negative
7	Not done	Negative	Negative	Negative
8	Negative	Isoechoic mass with hypoechoic rim	Negative	Negative
9	Negative	Hyperechoic mass	Negative but lipiodol accumulated	Negative
10	Not done	Hyperechoic mass	Mass of low density, positive enhancement	Negative

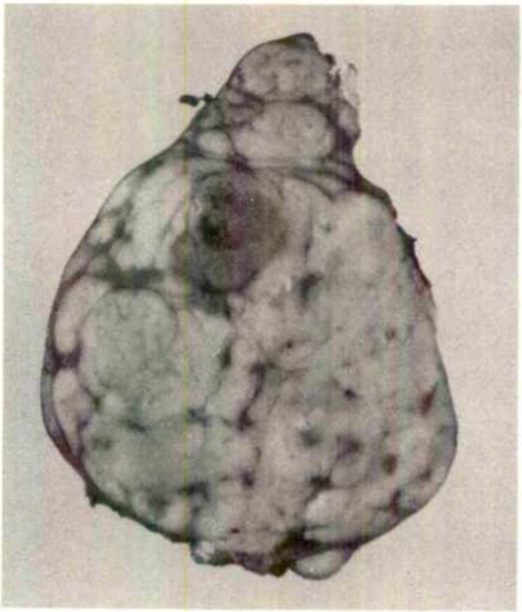


Figure 3 *Resected specimen in Case 4. The size of the pseudotumour was 3·1 × 3·1 × 3·1 cm. The dark nodule in the pseudotumour was histologically a hepatocellular carcinoma. Macronodular cirrhosis was present (upper part of the specimen)*

(0·8 × 0·8 × 0·8 cm) was discovered histologically in the pseudotumour (*Figure 3*). The maximal diameter of the pseudotumour was 1–1·9 cm in five, 2–2·9 cm in two, and ⩾ 3 cm in three cases. A pseudocapsule was present macroscopically in two patients. Hepatocyte proliferation was found in the pseudotumour of nine patients (cases 1–9). Liver cells with basophilic cytoplasm were observed in two specimens. In Case 10, the lesion consisted only of focal fatty cirrhosis surrounded by micronodular cirrhosis (*Figure 4*). Kupffer cells were present in all cases except one. Bile duct cells were found in the lesion of seven patients. *Figure 5* shows the carcinoma found in the pseudotumour in Case 4. Liver cirrhosis was present in all patients; it was micronodular in five, macronodular in three, and of a mixed type in two.

Survival

Five patients are alive, free of both hepatocellular carcinoma and pseudotumour. Two patients died of hepatocellular carcinoma and one is alive with this disease. Patient 5 died of hepatic failure 39 days after resection of hepatocellular carcinoma and pseudotumour. The oldest patient died of pneumonia 4 months after laparotomy (*Table 1*).

Discussion

Recent advances in the diagnostic methods used to detect hepatic tumours have increased our chances of detecting asymptomatic tumours of the liver. However, qualitative differentiation of space-occupying lesions is not necessarily easy, especially when the lesions are small. Close follow-up of patients with chronic liver disease allows a greater opportunity of finding hepatocellular carcinoma at a relatively early stage. One of the lesions to be differentiated from this carcinoma is regenerating hyperplastic nodule in the cirrhotic liver. We are not certain if our term hepatocellular pseudotumour is appropriate but most of these lesions mimic carcinoma clinically. Histology is the only reliable tool in diagnosis.

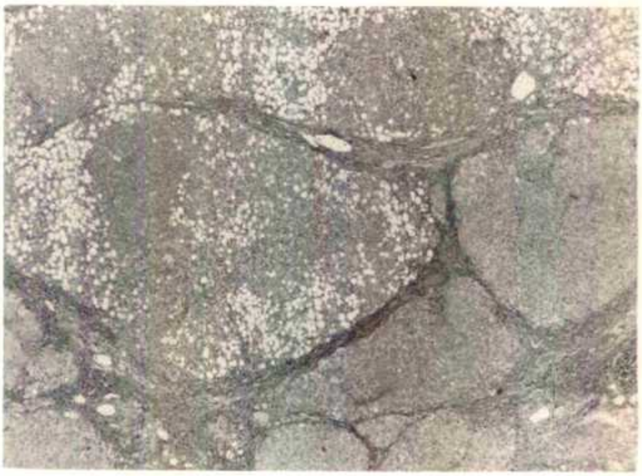
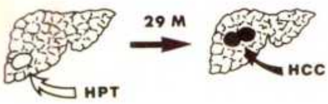
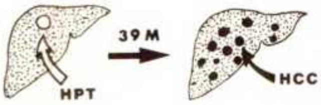
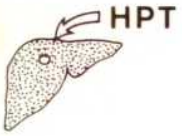
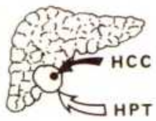
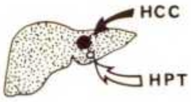
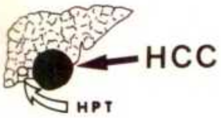
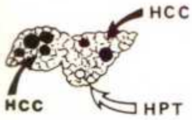
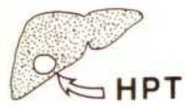
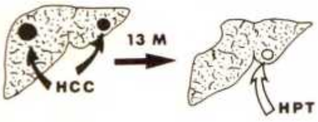
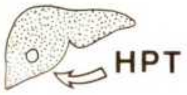


Figure 4 *Histological section of the lesion in Case 10. The lesion depicted by ultrasonography showed only focal fatty infiltration in a liver with micronodular cirrhosis (haematoxylin and eosin, original magnification: × 10)*

Of our ten patients, seven had hepatocellular carcinoma synchronously or metachronously with a pseudotumour. The most interesting was the fourth patient in whom a minute carcinoma was found in the resected pseudotumour (*Figure 3*). The lesion in this patient was detected only by ultrasonography. Such a radiological discrepancy is rare in hepatocellular carcinoma and we strongly suspected the mass to be a regenerating nodule. Similar cases have been reported recently by Arakawa *et al.*[6].

Liver cell dysplasia, which is characterized by cellular enlargement, nuclear pleomorphism with hyperchromasia and multinucleation of hepatocytes, has been proposed by Anthony *et al.*[7,8] as a precancerous lesion of the liver. Watanabe *et al.*[9] have recently suggested that the more important candidate is a collection of small dysplastic cells which often produces a small round focus. The nucleocytoplasmic ratio of such small dysplastic cells is between that of normal hepatocytes and that of hepatocellular carcinoma. In addition to these two lesions, Altmann[10] considers that a hyperplastic area with clear cells rich in glycogen is a precancerous state in non-cirrhotic livers. Neither the dysplastic cells described by Anthony *et al.*[7,8] and by Watanabe *et al.*[9], nor the clear cells rich in glycogen were

Table 3 *Pathological data of 10 patients with hepatocellular pseudotumour (HPT) in the cirrhotic liver*

Case No.	Correlation of HPT* with HCC	Size of HPT (cm) (pseudocapsule)	Microscopic findings of HPT	Type of liver cirrhosis	Histological type of HCC
1		3·2 × 3·0 × 2·5 (Absent)	Kupffer cells (+) Bile duct cells (+)	Mixed type	Not taken
2		2·5 × 2·5 × 2·5 (2–3 mm)	Basophilic cells (+) Kupffer cells (+) Bile duct cells (−)	Micronodular	Trabecular Edmondson II
3		2·0 × 1·6 × 1·5 (1 mm)	Kupffer cells (+) Bile duct cells (+)	Micronodular	
4		3·1 × 3·1 × 3·1 (Absent)	Basophilic cells (+) Kupffer cells (+) Bile duct cells (+)	Macronodular	Trabecular plus pseudoglandular Edmondson II
5		1·2 × 1·2 × 1·0 (Absent)	Kupffer cells (+) Bile duct cells (−) Fatty change (+)	Micronodular	Trabecular Edmondson II
6		1·7 × 1·5 × 1·5 (Absent)	Clear cells (+) Kupffer cells (+) Bile duct cells (+)	Macronodular	Trabecular Edmondson III
7		1·2 × 1·0 × 1·0 (Absent)	Kupffer cells (+) Bile duct cells (+)	Macronodular	Trabecular Edmondson II
8		3·0 × 2·5 × 2·0 (Absent)	Kupffer cells (+) Bile duct cells (+)	Micronodular	
9		1·9 × 1·7 × 1·4 (Absent)	Kupffer cells (+) Bile duct cells (+) Fatty change (+)	Mixed type	Trabecular Edmondson II
10		1·3 × 1·1 × 1·1 (Absent)	Focal fatty cirrhosis	Micronodular	

* HPT, hepatocellular pseudotumour; HCC, hepatocellular carcinoma

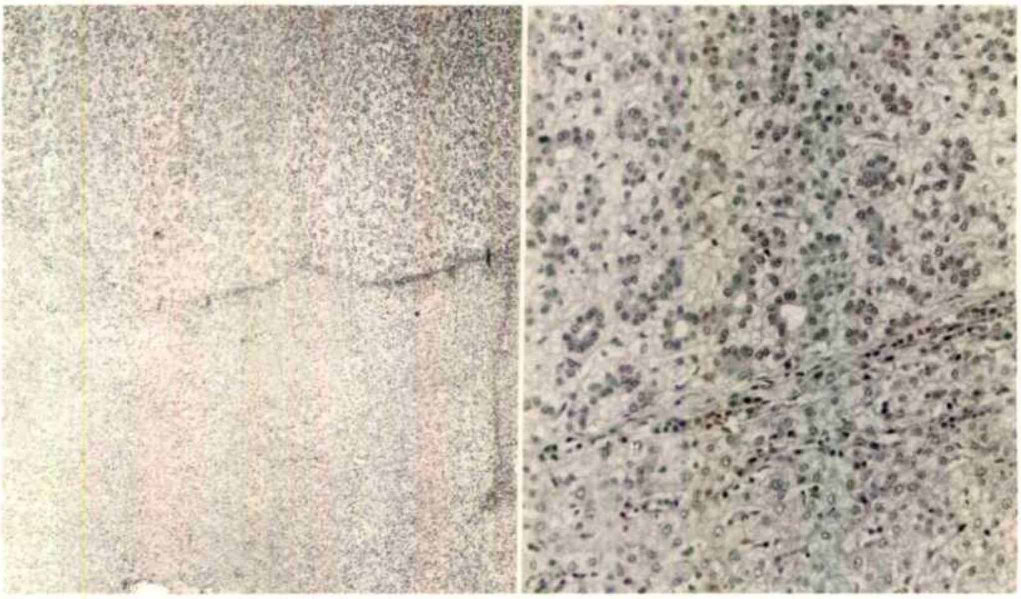


Figure 5 *Histological sections of the lesion in Case 4. The figures show the border portion of the pseudotumour and the hepatocellular carcinoma. Histological type of carcinoma was mostly trabecular but partly pseudoglandular (haematoxylin and eosin, original magnification: left × 10, right × 50)*

found in the pseudotumours of our patients, although in two cases the lesion was rich in basophilic liver cells, a finding which usually means active cellular proliferation.

At present we do not know if the development of carcinoma in the regenerating nodule in Case 4 was incidental or causally related. We do not assume that all such lesions detected on ultrasonographic follow-up of cirrhotic patients are related to hepatocellular carcinoma. The lesion appeared merely as a focal fatty infiltration in micronodular cirrhosis in Case 10, and such lesions can be detected as a hyperechoic lesion by ultrasonography. If these lesions are large enough, they will be depicted as cold areas by scintigraphy, as reported by Klion and Rudavsky[11]. The question may be whether or not the lesions presented herein are the same as 'macro-regenerating nodule in the cirrhotic liver' reported by Rabinowitz *et al.*[12]. The lesions in our and Arakawa's patients were approximately 3 cm or less and, as far as size is concerned, our lesions seem to be different from macro-regenerating nodules in the cirrhotic liver. At present it is difficult to state if this is a new entity or not. In the light of the current study it seems undeniable that hepatocellular carcinoma frequently develops in the cirrhotic liver with pseudotumour as we define it. We are beginning to appreciate some of the radiological and ultrasonographic characteristics of pseudotumours in the cirrhotic liver, but definitive diagnosis of this lesion is still difficult without histological studies. How to treat the patients with this lesion is a problem for further study.

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Obstructive pancreatitis: unusual causes of chronic pancreatitis

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Fifty-eight consecutive surgical pancreatic resections for chronic pancreatitis were examined. Eight cases were identified with obstructive pancreatopathy; all underwent pancreato-duodenectomy. Histological examination revealed that obstruction in three cases was due to duodenal wall cysts, and in two patients it was associated with pancreas divisum (the accessory papilla was obstructed by a neuroendocrine tumour in one case and by ectopic pancreatic tissue in the other). One case each was due to obstruction of an anomalous duct by vegetable matter, to segmental pancreatitis, and to an intraductal carcinoma. Obstructive pancreatitis has many causes and diligent pre-operative assessment is required as surgical resection may be beneficial. Special efforts should be made to identify ductal anomalies, duodenal cysts, ectopic pancreatic tissue, and small ampullary tumours of exocrine and endocrine origin in order to define the aetiology of pancreatitis.

Keywords: Obstructive pancreatitis, ectopic pancreatic tissue, duodenal cysts, pancreas divisum

In Western countries, chronic pancreatitis is precipitated by alcohol abuse in 60–85 per cent of patients[1]. Pancreatitis in the remainder is due to a variety of causes, classified as metabolic, obstructive, or manifestations of systemic disease. Despite exhaustive pre-operative investigation, the aetiology is not determined in some patients, and they are grouped under 'idiopathic' causes with its variable incidence of 9–45 per cent.

The revised Marseille classification of pancreatitis[2] drew attention to the importance of chronic obstructive pancreatitis. Firstly, it is the only form of chronic pancreatitis that will improve following definitive surgery to relieve the obstruction. Secondly, a wide range of lesions may lead to major duct obstruction including small tumours which may be surgically curable if resected early. Debate continues about whether failure of fusion of the dorsal and ventral pancreatic ducts (pancreas divisum) predisposes to an obstructive pancreatitis[3–5].

Obstructive pancreatitis is managed by relieving the obstruction when recognized. The accepted method of dealing with patients with pancreatitis and a dilated duct is pancreato-jejunostomy; this does not normally produce histological material and the cause of pancreatitis in these patients may remain unknown. In this report, the incidence and aetiology of obstructive pancreatitis has been examined in patients who underwent surgical resection between January 1984 and September 1986.

Patients and methods

Patient selection

The decision to operate was based on clinical criteria after consultation between physician and surgeon. These criteria included diagnostic certainty that chronic pancreatitis was the cause of symptoms, pain which was unrelieved by high doses of narcotics, repeated exacerbations of pancreatitis, weight loss and the development of complications.

Clinical investigation

A detailed history was taken to define the frequency of attacks of pancreatitis, length of history, age at onset, previous hospital admissions, amount of alcohol consumed, analgesic (including narcotic) consumption, weight loss and development of endocrine or exocrine insufficiency.

Laboratory investigation

A full blood count, determination of prothrombin time and biochemical profile was undertaken with specific tests for hypercalcaemia and hyperlipidaemia.

Imaging

Each patient first had an ultrasound examination. If the ultrasound failed to delineate the pancreas adequately, a computerized tomographic (CT) scan was performed. Features of obstructive pancreatitis were sought, specifically dilatation of the pancreatic duct upstream of a focal point with homogeneous atrophy of the parenchyma. Endoscopic retrograde pancreatography (ERP) was then attempted, taking care to examine both the major and minor papilla. If cannulation of the major papilla failed, an attempt was made to cannulate the minor papilla with the aid of intravenous secretin administration (50 units; Boots). If either papilla was abnormal a biopsy was taken and, if an abnormality was seen within the duct, biopsy of that abnormality or brush cytology was attempted. If the duct could not be cannulated, and duct diameter exceeded 3 mm on ultrasound examination, a percutaneous pancreatogram was attempted to delineate ductal anatomy. If obstruction was present and an abnormality was noted on ultrasound or CT scanning at the site of obstruction, fine needle aspiration biopsy of the abnormality was undertaken under ultrasound or CT guidance. Latterly an automated 'Tru-cut' biopsy was also performed. Finally, if further imaging was required, endoscopic ultrasound of the pancreas was performed using the Olympus 'Eloka' mk III endoscopic ultrasound apparatus.

Histological examination

After the specimen was resected, it was sent fresh for histological study. In relevant cases the duct system was demonstrated by injection of radio-opaque silicone rubber material (Micro-fil, Canton Bio-Medical products Inc, Colorado, USA) and soft-tissue X-rays were taken. The gland was then cut in coronal or sagittal planes into sections approximately 5 mm thick. Sections were formalin fixed and paraffin embedded in an orientated fashion. Histological 5 μm sections were stained with conventional haematoxylin and eosin stains and with routine immunoperoxidase stains to demonstrate the gut hormones insulin, glucagon, somatostatin, pancreatic polypeptide and gastrin. The general neural and neuro-endocrine markers neurone-specific enolase and protein gene product 9·5 (PGP 9·5) were demonstrated by an identical immunoperoxidase technique. The preponderance of pancreatic polypeptide in the islets of the ventral gland[6] was used to identify that part of the pancreas derived embryologically from the ventral pancreatic bud.

Results

Between 1 January 1984 and 30 September 1986, 58 patients underwent a pancreatic resection with a pre-operative diagnosis of chronic pancreatitis. There were 27 distal pancreatectomies, 21 Whipple's procedures (including pylorus-preserving pancreato-duodenectomies) and 10 total pancreatectomies. There was no 30-day mortality. The group consisted of 17 female and

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Table 1 *Details of the cases of obstructive pancreatitis*

Case no.	Age (years)	Sex	Alcohol (g/24 h)	Histology*
1	40	M	50–100	Duodenal wall cyst
2	63	M	<20	Duodenal cyst
3	37	M	<30 Previously >80	Periampullary cyst and ectopic pancreas at MP
4	50	F	Nil	Pancreas divisum Somatostatinoma at AP
5	24	M	<30	Pancreas divisum with ectopic pancreas at AP
6	33	F	Current 0 Previously >50	Wirsung duct obstructed by vegetable matter after pancreato-jejunostomy
7	59	M	<50	Segmental pancreatitis
8	60	M	<20	Intraductal papillary carcinoma

* MP, major papilla; AP, accessory papilla

41 male patients aged 4–76 years (median, 36 years). The eight cases of obstructive pancreatitis are listed in *Table 1*; all underwent resection of the head of the pancreas. Five of these cases are described below in detail to illustrate the heterogeneity of this group.

Case reports

Case 1

A 40-year-old man presented with recurrent attacks of acute pancreatitis. He consumed up to 100 g alcohol/day. He subsequently developed obstructive jaundice and underwent cholecystectomy and negative exploration of the common bile duct. Despite this the patient had further episodes of cholangitis and pancreatitis.

Ultrasound scan showed dilatation of the intrahepatic biliary tree. There was a complex cyst containing calcium in the head of the pancreas and dilatation of the main pancreatic duct. ERP demonstrated that the cyst did not communicate with the ductal system. At pancreato-duodenectomy there was a convoluted cystic space (approximately 1·5 cm in diameter and 6 cm long) within the head of the pancreas. Histology showed that the cyst was lined by inflammatory tissue and some areas of cylindrical epithelium suggesting a pancreatic ductal origin. There was moderate chronic pancreatitis. There was a similar cyst within the duodenal wall impinging on the ampulla of Vater (*Figure 1*).

Histological reconstruction suggested that the duodenal wall cyst caused obstruction of the pancreatic duct. A combination of the cystic mass and inflammation in the head of the pancreas led to obstruction of the common bile duct. The aetiology of the duodenal wall cyst is not clear but it is possibly the consequence of pancreatitis in ectopic pancreatic tissue. The significance of this patient's alcohol consumption remains unknown. Two similar cases were identified in the series.

Case 2

A 63-year-old man was referred for investigation of abdominal pain and jaundice. Biochemical investigation suggested resolving obstructive jaundice. Ultrasound showed a dilated biliary tree and at ERP an ampullary mass was found, consistent with an ampullary carcinoma. A pancreato-duodenectomy was performed. Histological examination revealed cystic changes similar to those in case 1.

Case 3

A 37-year-old man was referred for consideration of surgery because of chronic pancreatitis. He had a past history of heavy alcohol consumption (80 g/day). Ultrasound showed a heterogeneous pancreas with areas of calcification. The pancreatic duct was dilated to 6·5 mm and contained calculi. Pylorus-preserving pancreato-duodenectomy was performed. Histology confirmed marked chronic pancreatitis throughout the gland. There were numerous duodenal wall cysts present causing ductal obstruction.

Case 4

A 50-year-old woman was referred for further investigation of abdominal pain, weight loss and diarrhoea. The ultrasound scan showed that the dorsal and ventral pancreatic ducts appeared separate; the dorsal duct was dilated to 7 mm and the ventral duct was normal. ERP was attempted but failed at both papillae. The accessory papilla appeared unduly prominent and biopsy specimens were found to contain large quantities of neuroendocrine tissue. A percutaneous pancreatogram confirmed the presence of a dilated pancreatic duct with ectatic side branches and pancreas divisum.

The pre-operative diagnosis was of a neuroendocrine tumour of the accessory papilla and pancreas divisum. Pre-operative assays of gut hormones were normal. Pancreato-duodenectomy was performed. Macroscopically the accessory papilla protruded into the duodenal lumen and a 1·2 cm tumour occluded Santorini's duct; distal to this the pancreatic duct was dilated (*Figure 2*).

The tumour surrounded the intramural portion of the pancreatic duct, and appeared to have arisen from ectopic pancreatic tissue as several lobules of exocrine pancreas were recognizable around it in the duodenal wall. Immunohistochemical examination showed somatostatin positivity of the tumour cells. A local lymph node contained metastatic tumour. The remainder of the exocrine pancreas showed chronic pancreatitis with almost complete loss of exocrine tissue.

Case 5

A 24-year-old man was admitted with a 4-year history of abdominal pain. He had a past history of heavy alcohol consumption (200 g alcohol/day for 3 years). He had not drunk for 1 year before admission. ERCP revealed pancreas divisum with an equivocal dorsal pancreatogram. In July 1984 accessory pancreatic duct sphincterotomy was performed. Multiple further admissions for abdominal pain ensued and narcotic addiction developed. Pancreato-duodenectomy was performed. The dorsally derived pancreas showed mild periductal fibrosis consistent with chronic pancreatitis. Microscopic examination of the accessory papilla revealed ectopic pancreatic tissue surrounding the main pancreatic duct.

Case 6

A 33-year-old woman had a 6-year history of recurrent attacks of pancreatitis and had been a known alcohol abuser. She underwent pancreato-jejunostomy because of intractable pain. One year later the pancreato-jejunostomy was revised because of recurrent attacks of pancreatitis. Despite abstinence from alcohol her symptoms were unchanged. Two coeliac plexus blocks, a distal pancreatectomy and

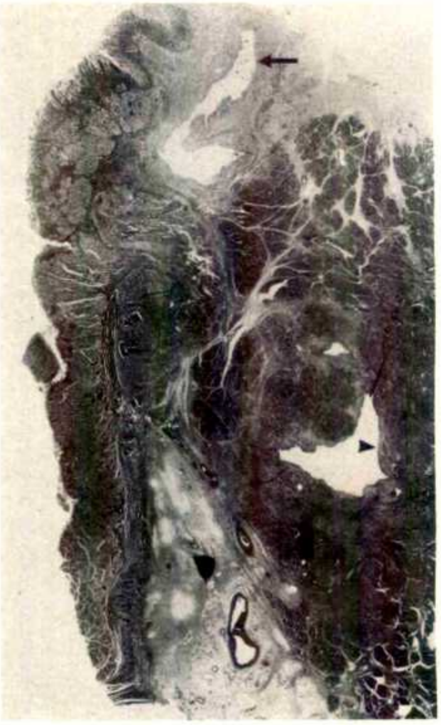

Figure 1 *Case 1: whole mounted coronal section through the head of the pancreas, including duodenal wall and major papilla. There are cystic spaces within the head of the pancreas (arrowhead) and within the submucosa of the duodenum below the papilla (arrow). Haematoxylin and eosin stain*

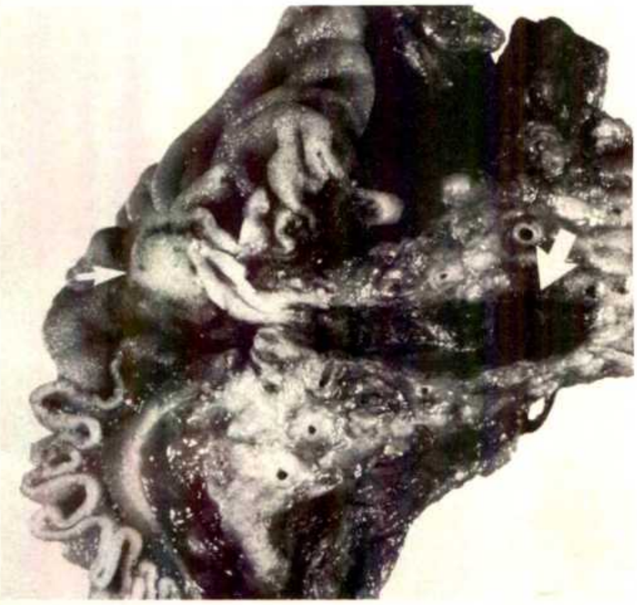

Figure 2 *Case 4: coronal section through the head of the pancreas and duodenum at the level of the accessory papilla showing a small tumour (small arrow) within the duodenal wall compressing Santorini's duct and causing ductal dilatation (large arrow)*

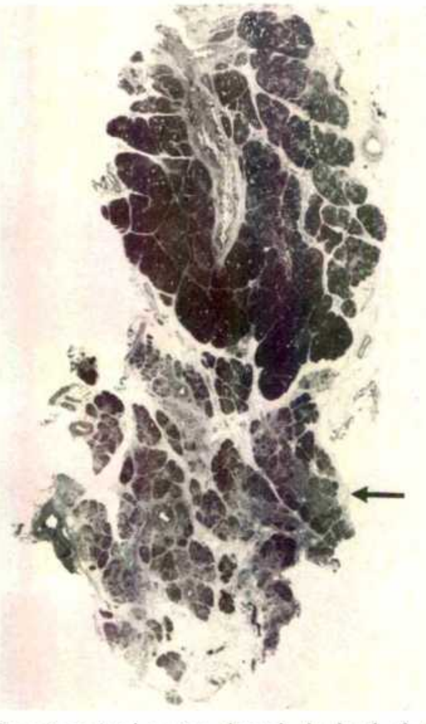

Figure 3 *Case 6: sagittal section through the head of the pancreas showing segmental pancreatitis involving the ventrally derived portion (arrow)*

finally operative insertion of a Silastic (Dow-Corning) tube into the pancreatic duct followed, all to no avail.

On admission to our care, abdominal ultrasound showed that the remaining pancreas appeared small with irregular parenchyma. There was no evidence of calcification or ductal dilatation. ERP failed at both papillae. Duodenum-preserving pancreatectomy was undertaken because of the severity of her pain.

Study of serial sections revealed that the entire pancreas drained via Santorini's duct. No communication was found between the main pancreatic duct and the major papilla. Histologically the dorsally derived pancreas showed mild inactive pancreatitis. The portion derived from the ventral anlage showed severe active chronic pancreatitis (*Figure 3*). The ventrally derived portion of the main pancreatic duct close to the confluence with the dorsally derived portion was constricted by periductal fibrosis and chronic inflammation. The ductal lumen was occluded by vegetable matter (*Figure 4*).

The duct of Wirsung in the head of the gland drained retrogradely in this patient into Santorini's duct. This variant occurred with a frequency of 0·9 per cent in the post-mortem series of Stolte[7]. In addition, the junction between the Wirsung and Santorini ducts was narrowed—one of the commonest sites for congenital strictures of the main pancreatic duct[8]. It is postulated that this patient initially had alcoholic pancreatitis and an unusual ductal anatomy. After pancreato-jejunostomy the dorsal duct was drained but the ventral duct was occluded by vegetable matter which gained access through the jejunostomy; obstructive pancreatitis then occurred in the ventral segment. Recurrent pancreatitis has been reported following retention of a splint in a pancreato-jejunostomy[8], and foreign bodies including vegetable matter have also been documented as a cause of pancreatitis when occluding pancreatic drainage[9].

Case 7

A 59-year-old man was referred with a 2-year history of intermittent right upper quadrant pain and $2\frac{1}{2}$ stone (≈15·75 kg) weight loss. During one attack of pain, hyperamylasaemia and mild obstructive jaundice were documented. An ultrasound scan showed multiple stones in the gallbladder and a dilated common bile duct.

ERP showed the dilated bile duct, revealed no stones but also showed a dilated pancreatic duct, findings interpreted as consistent with a small tumour obstructing the major papilla. Multiple biopsies of the papilla were performed but were histologically normal. A small ampullary tumour was thought to be the most probable diagnosis and pancreato-duodenectomy was performed.

The pancreas was small and fibrosed and the pancreatic duct was dilated to 5 mm. The gallbladder was markedly inflamed and fibrosed. Histological examination revealed ectopic pancreatic tissue around the intramural portion of Wirsung's duct and within the periampullary submucosa (*Figure 5*). The ventrally derived pancreas showed moderate fibrosing pancreatitis and duct dilatation. The retropancreatic portion of the bile duct was also involved in this process. The dorsally derived pancreas showed only mild fibrosis and no duct dilatation.

It is presumed that ectopic pancreatic tissue in the duodenal wall and major papilla led to obstruction of the main pancreatic duct and obstructive pancreatitis. It is also presumed that there must have been relative stenosis at the communication between Wirsung's duct and Santorini's duct, as the dorsal pancreas was relatively spared in the inflammatory process. It is concluded that this patient had a form of segmental pancreatitis predominantly affecting the posterior part of the head of the gland, that part closely approximated to the bile duct and embryonically derived from the ventral pancreas. Biliary disease is not usually considered relevant in the aetiology of chronic pancreatitis, but in cases with focal pancreatitis related to the bile duct it cannot be dismissed as an aetiological factor. It is also of note that, in the series of patients with 'pseudotumours' of the ampulla described by Leese *et al.*[10], significantly more of these patients had gallstones present than those with ampullary carcinoma.

Case 8

A 60-year-old man was referred with a 1-year history of recurrent attacks of acute pancreatitis. He was treated conservatively but lost one stone (≈6·3 kg) in weight in the subsequent year. Abdominal ultrasound examination showed dilatation of the pancreatic duct to a diameter of 10 mm in the head of the gland. The parenchyma was

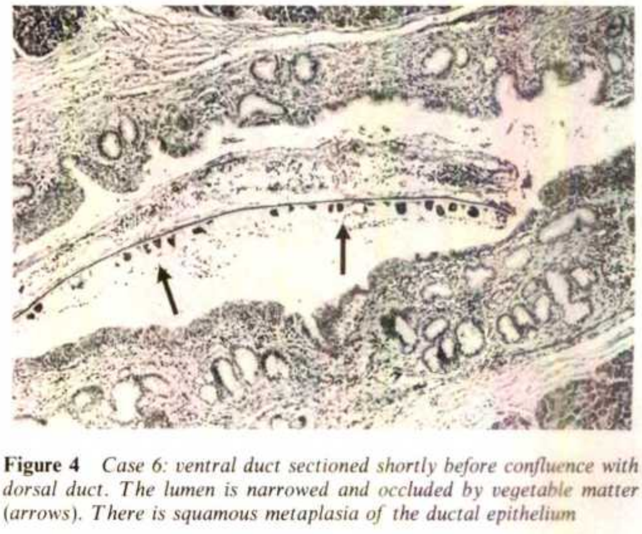

Figure 4 *Case 6: ventral duct sectioned shortly before confluence with dorsal duct. The lumen is narrowed and occluded by vegetable matter (arrows). There is squamous metaplasia of the ductal epithelium*

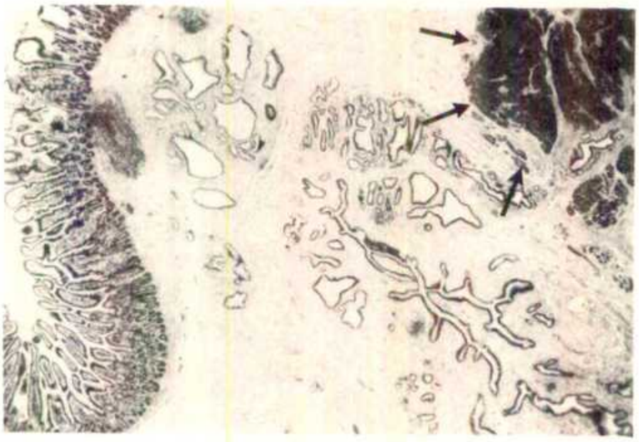

Figure 5 *Case 7: low-power micrograph of section through the major papilla, showing ectopic pancreatic tissue within the duodenal submucosa and involving the sphincter musculature (haematoxylin and eosin)*

atrophic in the head of the gland. There was a strongly echogenic focus at the point of obstruction. Endoscopic ultrasound examination suggested that the obstruction was either periductal fibrosis or, more probably, a small intraductal tumour (*Figure 6*). Computerized tomography confirmed these findings (*Figure 7*).

ERP revealed a serpiginous filling defect in the mid-duct. Biopsy and cytology were not diagnostic, and as tumour was considered the most probable diagnosis the patient underwent pylorus-preserving pancreato-duodenectomy.

Histological examination of the pancreas confirmed a dilated pancreatic duct with active chronic pancreatitis in the head and neck. The ventral duct near its junction with the dorsal duct was dilated and filled with a small villous adenoma showing moderate to severe dysplasia, with scanty mucin production. Several small ductules of moderately differentiated carcinoma were present surrounding the major duct near the adenoma with perineural invasion.

Discussion

The classification of pancreatitis was simplified at recent workshops into acute and chronic forms[2,11]. The Marseille classification drew attention to a special sub-group of patients with chronic pancreatitis, namely those with chronic obstructive pancreatitis. Morphologically, this is characterized by dilatation of the ductal system proximal to a point of occlusion, diffuse atrophy of the acinar parenchyma and uniform diffuse fibrosis. However, ductal dilatation may be a feature of other causes of chronic pancreatitis and is not pathognomonic. It is important to recognize this obstructive sub-group as these patients may obtain good results from surgical resection. The cause of obstruction may not be immediately apparent on pre-operative investigation and careful consideration must be given to the possibility of an obstructive aetiology, by a careful and detailed assessment. In addition, a significant number of cases that present clinically and radiologically as pancreatic malignancy are finally diagnosed as having benign obstructive pancreatopathy.

In this series we have found a variety of causes for pancreatic duct obstruction, some of which were not apparent pre-operatively despite detailed investigation.

Duodenal wall cysts

Duodenal wall cysts may be single or multiple, and may be submucosal or intramuscular. They are usually located on the mesenteric border of the first or second part of the duodenum. Typically the lining of the cyst is similar to the duodenal mucosa, although gastric and ectopic pancreatic tissue have been described[12,13]. Many aetiologies have been proposed, including duplications of the upper gastrointestinal tract, retention cysts of Brunner's glands and cystadenomas[13,14]. In advanced cases it can be difficult to determine the origin of the cyst. Duodenal wall cysts have been described as a cause of pancreatitis[12–15]. On the other hand, ectopic pancreatic tissue is said to be important in the development of duodenal wall cysts[12,16] and it is not clear if the cysts are the cause of pancreatitis or if pancreatitis affecting ectopic pancreatic tissue leads to cystic changes. A third possibility is that ectopic pancreatic tissue is more susceptible to pancreatitis and undergoes cystic change which leads to narrowing of the main pancreatic duct and obstructive pancreatitis.

Accessory papilla tumours

Somatostatinomas at both papillae have been described previously[17–19] although obstruction of the pancreatic duct was not observed. These reported cases had no evidence of diabetes or obstructive jaundice, except in one patient with coincident papillary carcinoma[19]. Somatostatinomas situated in the papillae may originate in the neuroendocrine component of ectopic pancreatic tissue. It is not yet possible to say w[illegible]r somatostatinomas are more common than other neuroendocrine tumours in this location.

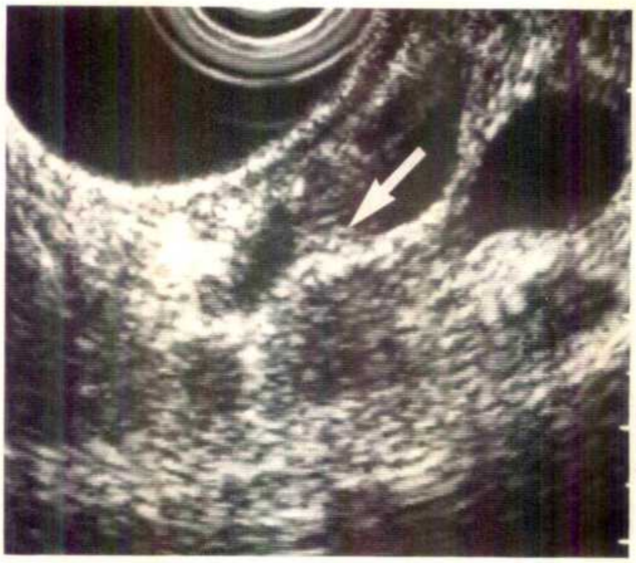

Figure 6 *Case 8: endoscopic ultrasound examination of dilated pancreatic duct segment. The duct wall is irregular and the lumen contains a soft-tissue density (arrowed) which is locally invasive papillary carcinoma*

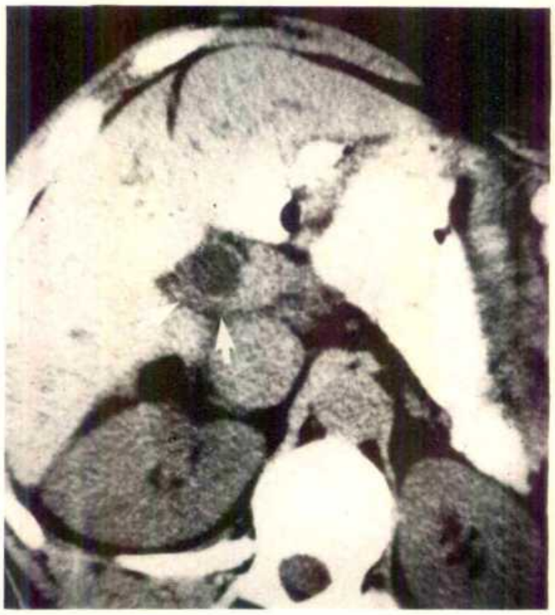

Figure 7 *Case 8: CT scan showing segmental dilatation of the main pancreatic duct in the neck of the pancreas. There is almost complete atrophy of the surrounding parenchyma (arrowed), but preservation of the parenchyma upstream*

Segmental pancreatitis

The ventrally derived part of the pancreas rotates posteriorly around the duodenum with the bile duct in the sixth week of embryonic development. Thus both the bile duct and the ventral pancreatic anlage lie posterior to the larger and dorsally derived pancreas. It is also more likely that pathological processes affecting the ventral pancreas will involve the bile duct because of their close approximation. The proximity of the pancreatic head to the bile duct and the duodenal loop suggest possible mechanisms in the aetiology of segmental pancreatitis, and biliary tract disease, duodenal ulcer, gastric surgery, duodenal wall cysts and ectopic pancreatic tissue in the duodenal wall have all been implicated. A retrospective study of segmental pancreatitis found that biliary disease was more common in this group of patients than in those with non-segmental pancreatitis[16]. Segmental pancreatitis was diagnosed in 24 per cent of a series of 123 pancreato-duodenectomy specimens[16]. It frequently mimics pancreatic carcinoma, as in the case reported here. Its true incidence is probably less than the above figure suggests as cases suspected of being malignant are operated on more frequently.

Leese *et al.* in their series of 49 patients of periampullary tumours identified 11 cases with so-called 'pseudotumours' of the ampulla with the endoscopic appearances of ampullary carcinoma but histological and clinical evidence of a benign process[10] In two of these eleven cases the histology was sufficiently disturbing to merit laparotomy. Their study highlights the difficulties in making a pre-operative diagnosis in patients with ampullary tumours and they advocate a policy of endoscopic biopsy and sphincterotomy initially, with repeat biopsy in all equivocal cases after inflammation has been allowed to resolve.

Ectopic pancreatic tissue

Ectopic pancreatic tissue is found most commonly in the second part of the duodenum close to the ampulla of Vater[20]. It has been associated with obstruction of the common bile duct[21] and a variety of symptoms relating to the upper gastrointestinal tract[22,23]. In the reported series of segmental pancreatitis, ectopic pancreatic tissue was noted in the duodenal wall in 3 of 30 cases but duodenal wall cysts were present in 17 of 30 cases[16]. As mentioned above, ectopic pancreatic tissue is considered to be an aetiological factor in the development of duodenal wall cysts.

Pancreatic carcinoma

Chronic obstructive pancreatitis due to carcinomatous duct obstruction is well described. The case described here is, however, slightly unusual. It is uncommon to detect papillary growths at ERP and most cases of pancreatic cancer are detected as strictures or abrupt blockage of the duct.

Ductal anatomy

Pancreas divisum is the commonest variant of ductal anatomy[3] and it remains controversial[3,5] whether this alone predisposes to obstructive pancreatitis. Pancreas divisum precludes the safety valve effect of two pancreatic ducts and may make an individual more susceptible to obstructive pancreatopathies of a more complex nature[24]. The site of fusion of the dorsal and ventral pancreatic ducts is commonly a point of narrowing[25] and may be the site of obstruction. If the pancreas drains via only one papilla, performing a distal pancreato-jejunostomy or sphincteroplasty may render the patient susceptible to duct obstruction by reflux of small bowel content, especially if the Roux loop used for the anastomosis is less than 40 cm long.

In conclusion, this study suggests that obstructive pancreatitis is not uncommon but has heterogeneous causes. Ectopic pancreatic tissue in the duodenal wall and particularly in relation to the papillae is probably more important in the pathogenesis of obstructive pancreatic lesions than has been recognized hitherto. It has been implicated in the development of duodenal wall cysts and segmental pancreatitis, and is also a potential site for both exocrine and endocrine neoplasia. Combined interpretation of clinical, radiological, ultrasonographic and histopathological data are required and even in these circumstances the true diagnosis may be made only on careful macroscopic and microscopic reconstruction of a surgical pancreato-duodenectomy specimen.

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Management of severe intra-abdominal sepsis: single agent antibiotic therapy with cefotetan versus combination therapy with ampicillin, gentamicin and metronidazole

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In a prospective, randomized trial involving 100 patients with severe intra-abdominal sepsis, the value of single agent antibiotic therapy with cefotetan was compared with that of combination therapy of ampicillin, gentamicin and metronidazole (AGM). All patients underwent exploratory laparotomy. The mortality rate was 3 per cent, all deaths occurring within 48 h of operation. Two-thirds of patients were considered severely ill on admission, and one-third were moderately ill. Six patients had positive blood cultures on entry into the study. The mean age was 31 years and concurrent disease was present in 14 per cent of the patients. A satisfactory response was achieved in 82 per cent of patients receiving cefotetan and in 65 per cent of those receiving AGM, whereas the response was unsatisfactory in 18 per cent of cefotetan patients and 35 per cent of those receiving AGM ($P = 0{\cdot}075$ *n.s.*). *Significant changes in laboratory values during the study occurred in 51 per cent of patients, and 7 per cent required vitamin K administration for hypoprothrombinaemia. The results of this study suggest that antibiotic therapy with single agent cefotetan is as safe and effective as a combination of ampicillin, gentamicin and metronidazole in patients with severe intra-abdominal sepsis requiring operative management.*

Keywords: Intra-abdominal sepsis, peritonitis, antibiotic treatment

Successful management of intra-abdominal infection is based on the following principles. Operative intervention achieves removal of the source of contamination, debridement of devitalized tissues and drainage of pus. Systemic complications, as manifested by organ dysfunction, require supportive management. Antibiotic therapy is regarded as an adjuvant measure against bacterial invasion, in that it is synergistic with the host's own immune defence mechanisms.

Mortality rates quoted in the literature vary considerably, reflecting lack of standard criteria in reporting this complex problem. As well as several elements of surgical technique, optimal antibiotic therapy remains controversial. The ideal agent should be effective against all the pathogens commonly encountered, free from toxic side-effects, inexpensive and convenient to administer Most investigations support the view that the antibiotic should be directed against both the aerobic and anaerobic components of the intra-abdominal flora, and combinations of an aminoglycoside, metronidazole and a penicillin derivative have become standard. Newer agents with a wider spectrum of activity have now become available The development of 'second' and 'third' generation cephalosporins and ureido-penicillins has fuelled the search for less toxic, but equally effective preparations Various comparative clinical trials have been conducted but substantial differences in treatment results have not generally been forthcoming[1–10].

Cefotetan is a recently developed semi-synthetic cephamycin active against most organisms commonly isolated from intra-abdominal infection, including *Escherichia coli* and many of the *Bacteroides fragilis* organisms Its antibacterial spectrum, pharmacokinetics and low toxicity make it a potentially attractive antibiotic for the treatment of intra-abdominal sepsis. The present study compares the efficacy of cefotetan with that of a combination of ampicillin, gentamicin and metronidazole (AGM) in a prospective, randomized trial in patients requiring operation for serious intra-abdominal infection.

Patients and methods

Patient selection

Patients older than 14 years who were admitted to King Edward VIII Hospital, Durban, between July 1985 and October 1986 and who required surgical management for intra-abdominal sepsis were eligible for the study. The study protocol was approved by the Hospital Ethics Committee in accordance with the Declaration of Helsinki, 1964 Not eligible were patients with a known allergy to the antibiotic agents, pregnant or lactating women, patients receiving concurrent antibacterial or other investigational drugs and those who appeared moribund and unlikely to survive operation. Informed consent was obtained from all patients and randomization achieved by means of a sealed code block chart Once admitted to the study they were evaluated by physical and laboratory criteria before operation, during treatment after operation, at conclusion of antibiotic therapy, and during follow-up 1–4 weeks later All consecutive patients admitted to two of the six surgical units at King Edward VIII Hospital were considered for inclusion in the study and this cohort represents one-third of all patients with intra-abdominal infection admitted over the 16-month study period

Antibiotic therapy

Randomization was either to treatment with cefotetan or with ampicillin, gentamicin and metronidazole (AGM). Cefotetan disodium, (Apatef, ICI Pharmaceuticals Ltd.), a sterile lyophilized powder was dissolved in water for injection (BP) to a strength of 2 g in 10 ml and administered intravenously as a slow bolus dose 12 hourly. Gentamicin (80 mg 8 hourly), ampicillin (1 g 6 hourly) and metronidazole (500 mg

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Table 1 *Sex and age of 96 patients in the study*

	Antibiotic therapy	
	Cefotetan	AGM
Male	36	36
Female	11	13
Mean (±s.d.) age (years)	29·2 (±13·4)	32·5 (±14·9)
Median age (years)	28	31
Range	(14–65)	(14–71)

AGM, ampicillin, gentamicin, metronidazole; s.d., standard deviation

8 hourly) were given intravenously. After 48 h the intravenous administration of metronidazole was changed to rectal suppositories 1 g every 8 h. The first antibiotic doses were given before operation and therapy continued afterwards for 5–10 days, depending on clinical progress. In patients with impaired renal function, cefotetan dosage was reduced by increasing the administration interval. Similarly, gentamicin peak levels were monitored in patients with raised serum creatinine levels. Any other non-antibiotic medication thought to be essential for the medical management of the patient was continued and recorded.

Microbiology

Blood and urine specimens were obtained for culture before starting antimicrobial therapy. Blood was collected aseptically after skin antisepsis and was inoculated into culture media for aerobic and anaerobic incubation (Bactec media 6B and 7D, Johnston Laboratories, USA).

At operation, specimens of any pus, inflammatory exudate or bile collections were sampled. When possible, 5–10 ml of fluid were aspirated into a sterile syringe; thereafter any air was expelled and the needle capped with a sterile rubber stopper. In addition swab specimens were collected and placed deeply in Stuart's transport medium.

All specimens were appropriately identified and forwarded without delay to the microbiology laboratory for processing.

Blood cultures were incubated at 37°C and examined visually and radiometrically for growth on days 1, 2, 3, 5 and 7 after receipt. Cultures yielding growth were subcultured immediately and investigated further. Catheter urine specimens were inoculated on to cysteine–lactose electrolyte-deficient medium (CLED, Oxoid, UK) using a standard loop. Bacterial counts were determined after overnight incubation at 37°C. Counts of bacteria $> 10^5$/ml of a single or predominant species were considered significant.

Smears were prepared for Gram staining and microscopy from syringe and swab specimens, which were also inoculated on to the following media: MacConkey agar for incubation in air, 5 per cent blood agar for incubation in air plus 5 per cent carbon dioxide, thioglycolate broth and 10 per cent brucella blood agar enriched with vitamin K and haem, with and without amikacin 100 mg/l for incubation in an anaerobic chamber (Forma Scientific, USA). Aerobic and facultative bacteria were identified by standard methods. Anaerobic bacteria were identified using the Minitek system (BBL Microbiology Systems, USA). Gram-tube test-positive yeasts were identified as *Candida albicans*. Other yeasts were identified using the API 20 C system (API System SA, France). Antimicrobial susceptibilities for bacterial isolates were determined by the disc diffusion method of Stokes and Waterworth[11].

Data collecting

Patients were assessed clinically every day and their progress monitored. The response was considered satisfactory if treatment resulted in normalization of haemodynamic and respiratory values, return of intestinal activity, disappearance of signs of intra-abdominal sepsis and fever, clearing of the sensorium and subjective well-being. Blood samples were obtained before, during and after therapy for haematological, renal and liver function tests. After operation microbiology specimens were collected from any drain site, wound, urine, blood, sputum or during re-laparotomy on suspicion of sepsis. Adverse events were recorded and special attention paid to any bleeding tendency. An increase in prothrombin time of 5 s or more during the study, or a value in excess of double the control value on entry, was treated by means of 10 mg vitamin K injection daily and closely monitored by haemostatic tests.

Final outcome and statistical analysis

The outcome was reported in a stratified manner as suggested by others[8,9], the end result being either death or survival, and the control of disease considered satisfactory, unsatisfactory or indeterminate. Although successful treatment in bacteriological terms means 'eradication' of the causative micro-organisms, and 'failure' the lack of this, reporting on the outcome of intra-abdominal sepsis is essentially clinical as the peritoneal cavity is not normally accessible for follow-up microbiology specimens. Therefore a clinically satisfactory response was equated with elimination of the offending organisms. Recurrent or continuing sepsis in the abdomen or abdominal wall, or septic complications arising outside the peritoneal cavity (chest or urinary tract infection) were considered an unsatisfactory response both in clinical and microbiological terms.

Statistical analysis of data was by means of Student's t and χ^2 tests, the level of significance being 5 per cent.

Results

A total of 100 patients was initially randomized, but 4 were subsequently withdrawn; 3 failed to meet protocol requirements, and 1 was withdrawn in error. Therefore 96 patients were available for analysis, 47 of whom received cefotetan and 49 AGM. The sex and age distribution in the two groups are shown in *Table 1*. All patients underwent exploratory laparotomy through a midline abdominal incision and at the end of operation the peritoneal cavity was copiously lavaged with saline. All skin wounds were managed by delayed primary closure. The anatomical sites of origin of the infection are shown in *Table 2*. More patients with upper gastrointestinal tract involvement were randomized to treatment with AGM than with cefotetan, whereas the reverse applied to the appendix and colon. All perforations of stomach and duodenal ulcers had existed for more than 12 h and the patients presented with fibrinopurulent peritonitis. Patients with appendicitis were only included if rupture and generalized peritonitis were present. Most of the relatively large number of small bowel disruptions resulted from either blunt or penetrating abdominal trauma, the patients reaching hospital with considerable delay. On the basis of clinical assessment and early laboratory data, 66 (69 per cent) patients were considered severely ill on admission. Their peritonitis had existed for more than 24 h, they required more than 4 litres of fluid for resuscitation and were tachypnoeic, hypoxic and acidotic with a clouded sensorium. On similar grounds 30 patients (31 per cent) were considered moderately ill. Six patients had positive blood cultures on admission (*Streptococcus faecalis*, *Streptococcus morbillorum*, *Staphylococcus epidermidis*, diphtheroids, *Salmonella typhi* and *Klebsiella oxytoca*). Concurrent disease was recorded in 14 patients (*Table 3*). The mean duration of antibiotic administration was 5·2 (±1·8) days for cefotetan and 6 (±2·2) days for AGM. Mean total doses of antibiotics given were cefotetan 22·4 g, ampicillin 16·4 g, gentamicin 1·3 g and metronidazole 10·3 g. The standard deviations in mean total dose were greater for AGM than for cefotetan (*Table 4*).

The final outcome is summarized in *Table 5*. Three patients died within 48 h of the start of treatment. One patient had

Table 2 *Site of origin of intra-abdominal infection*

	Antibiotic therapy	
Site	Cefotetan	AGM
Stomach/duodenum	7	12
Gallbladder/biliary tract	0	2
Small bowel	12	17
Appendix	17	10
Colon	6	3
Pancreas	1	0
Liver	2	1
Gynaecological origin	1	3
Other	1	1
Total	47	49

AGM, ampicillin, gentamicin, metronidazole

Table 3 *Concurrent disease*

Disease	Antibiotic therapy	
	Cefotetan	AGM
Respiratory	1	2
Cardiovascular	2	1
Gastrointestinal	2	1
Genito-urinary	1	0
Malignancy	1	0
Diabetes mellitus	2	1
Total	9	5

AGM, ampicillin, gentamicin, metronidazole

Table 4 *Antibiotic administration duration and dose*

	Antibiotic therapy	
	Cefotetan	AGM
Mean (±s.d.) days	5·2 (±1·8)	6·0 (±2·2)
Range in days	3–8	3–9
Mean (±s.d.) total dose (g)	22·4 (±6·9)	16·4/1·3/10·3 (±8·3/0·5/3·8)

AGM, ampicillin, gentamicin, metronidazole; s.d., standard deviation

suffered penetrating abdominal injury with bowel and liver perforation 24 h before admission. She died in septicaemic shock soon after operation. *E. coli* and *Klebsiella pneumoniae* were isolated from the intraperitoneal pus. Her blood culture yielded no growth. The second patient sustained a gunshot injury to his chest and abdomen and was operated on some 16 h later. He had a haemopneumothorax, lacerated diaphragm and transverse colon, and paraplegia and died the next day in the intensive care unit in septicaemic shock with evidence of disseminated intravascular coagulation. *E. coli*, *Streptococcus faecalis*, *Clostridium perfringens* and *Bacteroides* sp. were isolated from the peritoneal cavity, but the blood culture was negative. The third patient died following inhalation of gastric contents the day after operation had been undertaken after a 16 h delay following perforation of the small bowel. *E. coli* and *C. albicans* were isolated from his peritoneal cavity. His blood culture was negative.

Of the 97 surviving patients, 65 had a satisfactory response (cefotetan 37, AGM 28) and 23 an unsatisfactory response (cefotetan 8, AGM 15). Wound infections occurred in 11 patients during their stay in hospital and afterwards until 6 weeks after operation, and respiratory or urinary tract infection developed in 10. In one patient *Salmonella typhi* infection failed to respond to cefotetan and chloramphenicol was given instead. In another patient receiving AGM, a sub-phrenic abscess was drained after initial partial gastrectomy for perforated gastric ulcer. *E. coli* was isolated on both occasions.

In nine patients the response was not determined. Three failed to meet the protocol requirements and one was erroneously withdrawn. Three other patients developed respiratory failure and required prolonged ventilatory support. Because of colonization with resistant organisms in the intensive care unit, other antibacterial and antifungal agents were given. One patient was operated on for traumatic gastric perforations and received AGM. *Klebsiella ozaenae*, *Citrobacter freundii* and *Aeromonas hydrophilia* were isolated from the peritoneal pus. In addition he was found to have active pulmonary tuberculosis and therefore was treated with rifampicin and streptomycin. Another patient underwent a small bowel repair after sustaining blunt abdominal trauma 4 days before. He was treated with AGM, but the gentamicin was discontinued because of severe renal failure requiring haemodialysis (serum creatinine level 1856 μmol/l and urea 73·4 mmol/l).

Although the patients receiving cefotetan had a more favourable course then those receiving AGM, the difference was not statistically significant (*Table 5*).

Changes in laboratory values during the study occurred in 51 patients and are summarized in *Table 6*. Vitamin K was administered to four of nine patients, who had developed an increase in prothrombin time during antibiotic treatment. No episodes of abnormal bleeding were encountered in either group.

The bacteriological data are summarized in *Table 7*. *E. coli*, *Klebsiella* sp., *Proteus* sp., streptococci, *Bacteroides* sp. and clostridia were most commonly encountered, with comparable distribution in both treatment groups. Thirty-six patients had more than one organism cultured from their peritoneal cavity, the combination of *E. coli* and *Bacteroides* occurring in 24 instances. In 17 patients the organisms could not be identified. *Saccharomyces cerevisiae* ('brewers' yeast') was isolated in 10 of the 19 patients with gastroduodenal perforations.

Discussion

Intra-abdominal infection secondary to abdominal injury or diseases of the alimentary tract carries a significant morbidity and mortality. However, outcome studies in the management of intra-abdominal infection have yielded a broad range of results. Published comparisons of antibiotic therapy in patients with intra-abdominal infection have tended to report relatively low morbidity and mortality rates and high degrees of antibiotic

Table 5 *Stratified outcome in 100 patients operated for intra-abdominal sepsis*

Outcome	Antibiotic therapy	
	Cefotetan	AGM
1 Died:		
A) Related to sepsis (death >48 h)	—	—
B) Related to sepsis (response not determined, death <48 h)	1	2
2. Survived:		
A) Satisfactory response	37	28
B) Unsatisfactory response	8	15
—antibiotic changed	1	—
—recurrence intra-abdominal sepsis	—	1
—wound infection	3	8
—LRTI	4	5
—UTI	—	1
C) Indeterminate	4	5
—failed to meet protocol requirements	2	1
—withdrawn in error	1	—
—other (therapy modified)	1	4
3 Evaluable for outcome (1A + 2A + 2B)	45	43
Total	50	50

AGM, ampicillin, gentamicin, metronidazole; LRTI, lower respiratory tract infection, UTI, urinary tract infection

Table 6 *Significant changes in laboratory values during study*

Parameter	Antibiotic therapy			
	Cefotetan		AGM	
	n	%	*n*	%
Albumin	14	31	11	26
Bilirubin	2	4	2	5
AST	6	13	3	7
Creatinine	1	2	3	7
Prothrombin time	7*	16	2†	5

* Vitamin K given to 3, † Vitamin K given to 1; AGM, ampicillin, gentamicin, metronidazole; AST, aspartate transaminase

Table 7 *Bacteriology of cultures obtained from peritoneal cavity with the number of organisms isolated*

	Antibiotic therapy	
Organism	Cefotetan	AGM
Anaerobic		
Bacteroides fragilis group	4	3
Bacteroides sp.	24*	16†
Fusobacterium sp	1	0
Clostridium sp.	7	6
Non-sporing Gram-positive bacilli	1	0
Peptostreptococci sp.	1	0
Aerobic Gram-negative		
Escherichia coli	14*	20†
Citrobacter sp.	3	4
Enterobacter sp	3	4
Klebsiella sp.	6	11
Proteus mirabilis	3	3
Proteus sp	1	2
Pseudomonas aeruginosa	1	4
Pseudomonas sp	0	1
Salmonella typhi	1	0
Haemophilus influenzae	0	1
Aeromonas sp.	0	1
Aerobic Gram-positive		
Streptococcus milleri	5	4
Streptococcus faecalis	5	2
Streptococcus viridans	0	3
Streptococcus sp.	11	2
Staphylococcus epidermidis	2	0
Corynebacterium sp	1	0
Bacillus sp.	0	1
Yeasts		
Candida albicans	4	4
Saccharomyces cerevisiae	3	7
Other yeasts	3	3

*Combination *E Coli*+*Bacteroides*=11; †Combination *E Coli*+*Bacteroides*=13; AGM, ampicillin, gentamicin, metronidazole

success[1,9,10,12], in contrast to reviews of intra-abdominal infection focusing on risk factors and operative techniques, many of which report substantially higher rates of morbidity and mortality[13–17]. Therefore, it seems that there is a lack of uniformity in reports of intra-abdominal infection emanating from different centres, the reports describing different diseases, processes and patients. The severity of illness as well as underlying disease are important determinants of outcome in septic patients and these can be objectively assessed[13–15,18–20]. A most accurate predictor of outcome is the APACHE II score recently developed by Knaus *et al.*[21]. Studies of intra-abdominal sepsis should ideally include operative confirmation of the diagnosis, which was available for all patients in our series.

Successful treatment ultimately depends on prompt adequate operative management with appropriate supportive care. Antibiotics assume a secondary role in the management of this complex disease entity. The intraperitoneal infection is usually polymicrobic and commonly consists of an aerobic component, associated with early mortality, and an anaerobic component, responsible for later septic complications[16,22,23]. The commonest organisms are *E. coli* and *Bacteroides fragilis* and the antibiotic agents should be active against them. Combination chemotherapy is widely used. Metronidazole is very active against anaerobes and gentamicin is active against *E. coli* and many other Gram-negative facultative aerobes. Ampicillin provides additional cover against enterococci, *Proteus mirabilis* and *Salmonella* sp. Few side-effects occur with metronidazole and ampicillin, but renal dysfunction has been recorded in 5–25 per cent of patients receiving gentamicin[12,24,25] illustrating the need to monitor peak and trough levels of this agent. The development of newer cephalosporins has resulted in increasingly wider spectra of activity, making them suitable for use as single agents. Cefotetan is a third generation cephalosporin, highly stable to hydrolysis by β-lactamases and active against most intra-abdominal micro-organisms, including *E. coli* and *Bacteroides* sp., but inactive against *Streptococcus faecalis* and *Pseudomonas aeruginosa*. It has a plasma $t_{\frac{1}{2}}$ of 4 h, and trough levels 12 h after a 2 g intravenous injection are greater than the minimum inhibitory concentration for 90 per cent of the commonest organisms, which makes it suitable for twice daily administration[26]. It is reportedly free of nephrotoxic effects or interference with haemostasis in daily doses up to 4 g[27,28].

Published reports of antibiotic comparisons have largely failed to demonstrate noteworthy differences in clinical outcome despite markedly disparate antibiotic sensitivity spectra[9] It is not surprising, therefore, that the results of our study are not dissimilar. A few factors may have contributed to our low mortality of 3 per cent. Advanced age is a heavily weighted determinant of fatal outcome[14,20,21] and the mean age of the patients in our study was only 31 years Few had concurrent disease, probably a reflection of their relative youth. Diabetes, alcoholic liver disease, neoplasia and malnutrition are clinical risk factors associated with increased mortality[14,20,21]. Approximately one-quarter of our patients had appendix-related peritonitis, which tends to carry a lower mortality[20].

The optimal duration of antibiotic treatment is not established. The mean duration in this study was 5–6 days but much longer courses are used elsewhere[29,30]. The surgeon should be guided by signs of clinical well-being such as a soft, non-distended and non-tender abdomen with return of normal peristaltic activity and a subsidence of fever and leucocytosis. Cefotetan was administered accurately in a convenient twice daily regimen, but the combination treatment was flawed with various administrative errors, as illustrated by the standard deviations of the mean total doses. Antibiotic monotherapy in busy surgical wards is preferable to combination therapy.

In comparative antibiotic studies, initial identification of the causative organisms followed by proof of their subsequent elimination is the ideal method of antimicrobial assessment. However, follow-up specimens from the peritoneal cavity are not normally available unless reoperation is performed. Cultures from indwelling drains are unreliable as these rapidly become colonized after insertion. Therefore assessment must be mainly clinical

The outcome in this study has been stratified in accordance with criteria outlined by others[8,9,20]. The endpoint of any treatment is either death or survival. Return to baseline condition before illness and no recurrence of sepsis within the follow-up period is a valid criterion for satisfactory response. Such a response was achieved equally well in patients treated with cefotetan or with the combination of AGM.

Third generation cephalosporins have been associated with an increase in enterococcus superinfection[31] In the cefotetan group *Streptococcus faecalis* was cultured from the infected wound in only one patient; this organism was also initially present in the peritoneal cavity.

The ability of third generation cephalosporins to produce coagulation disturbances due to hypoprothrombinaemia and/or platelet dysfunction has been reported recently[32,33]. Significant changes in prothrombin time occurred in seven patients treated with cefotetan as against two treated with AGM. In only three patients was the abnormality such that vitamin K administration was needed as against 1 patient receiving AGM There were no bleeding episodes as a result of these prothrombin time changes. Various other abnormalities in laboratory parameters were recorded, notably in serum albumin concentrations. These no doubt reflect the profound metabolic changes occurring during peritonitis.

This study has demonstrated that broad spectrum single agent antibiotic chemotherapy with cefotetan is as effective as combination therapy with ampicillin, gentamicin and metronidazole in the management of intra-abdominal sepsis. Few adverse effects were encountered. However, antibiotic therapy alone is inadequate for severe intra-abdominal sepsis, and it thus remains an adjunct to appropriate surgical intervention and supportive management of organ dysfunction.

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Splenic repair for trauma

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The risks of overwhelming post-splenectomy infection (OPSI) are now well documented both in children and adults. Although the incidence of OPSI is comparatively low following splenectomy for trauma, it has a high mortality. Splenectomy is no longer the treatment of choice for splenic injury and splenic salvage is recommended whenever feasible. Since 1982, in the Isle of Wight hospitals, 13 cases of splenic injury following trauma have been treated applying various salvage procedures and are reported here.

Keywords: Splenic, trauma, repair, preservation

Splenectomy following trauma, regardless of the extent of the injury to the spleen, has been standard procedure over the last two centuries[1]. About a quarter of all splenectomies are done because of operative injury or are incidental to another procedure[2]. In 1919, Morris and Bullock, after animal experiments, suggested that the human body deprived of splenic function would show an increased susceptibility to infection[3] but it was not until 1952 that King and Shumacker reported increased risks of and deaths from infection in splenectomized infants[4]. The risks of overwhelming post-splenectomy infection (OPSI) related to splenectomy performed at any age and for any reason are now clearly documented[5,6]. The risks of OPSI following splenectomy for trauma are reported between 1 and 2 per cent[7]. This occurrence of severe sepsis is 50–200 times more than is expected in the population at large and carries very high mortality[8,9].

Patients and methods

Since 1982 in the Isle of Wight hospitals one surgical team has adopted a prospective policy of splenic conservation following splenic trauma whenever feasible Thirteen consecutive cases of post-traumatic splenic injury have been treated by various salvage procedures and are reported here

The average age of the patients was 24 years (5–55 years) Ten were men and three women. One case was due to penetrating injury The rest were due to blunt abdominal trauma. Six patients had additional injuries. All patients, after initial resuscitation, underwent a laparotomy under general anaesthesia. The average volume of intraperitoneal blood and clots was 1450 ml (50–4900 ml) The spleen was mobilized and thoroughly examined. In five patients (four with simple lacerations and one with penetrating injury to the upper pole) the splenic bleeding was found to have virtually stopped The nature of the injuries to the spleen and methods of repair used are summarized in *Table 1*. After repair complete haemostasis was achieved and rechecked at least 5 min later before closing the abdomen. Left subdiaphragmatic drains were used in four cases.

Results

Twelve out of thirteen patients achieved an excellent result from splenic repair and in this group there were no immediate or late postoperative complications related to the abdominal operation or splenic repair after a mean follow-up of 32 months (4–70 months).

The thirteenth patient had multiple lacerations of the spleen and a shattered pole. He was treated initially by mattress suture of the lacerations, partial splenectomy and omental wrapping of the spleen but required re-exploration 6 h later because of persistently low blood pressure. At this second operation there was slow oozing over the partial splenectomy site and a total splenectomy was carried out. This patient, who was deeply unconscious from the time of the injury, also had a cerebral shearing lesion with cerebral infarction, severely contused left lung and multiple limb fractures. He died from irreversible primary brain damage on the sixth postoperative day

Discussion

Many alternatives to splenectomy for trauma are well established[10,11]. Non-operative treatment can be safe if great care is taken with patient selection and observation with computed tomography and radioisotope scans is readily available[12,13]. These investigations were not immediately available on the Isle of Wight and a policy of surgical exploration was adopted in all cases. With all operative techniques of splenic preservation it is essential to mobilize carefully and inspect the spleen as a whole after gently removing all the clots, so that a complete assessment of the nature and extent of the injury can be made. Minor lacerations or capsular tears, where bleeding has almost completely stopped, only require pressure and application of topical haemostatic agents. More severe lacerations may be treated with absorbable mattress sutures over a patch of omentum or haemostatic agent. The lacerated spleen may also be wrapped in omentum or polyglycolic mesh or compressed within a catgut suture ladder to achieve haemostasis Partial splenectomy is reserved for polar injuries or when only part of the spleen is damaged beyond repair. The effectiveness of deliberate autotransplantation following unavoidable total splenectomy remains controversial[14,15].

Published reports indicate that operative time and intraoperative blood loss are not increased when splenic repair is compared with splenectomy[12,16,17]. The incidence of rebleeding following splenic repair is rare. From a total of 569 documented cases of splenic repair[12,16–25] a second laparotomy for re-

Table 1 *The nature of injuries to the spleen and methods of repair*

Nature of injuries	No	Type of repair	No.
Simple lacerations	6	Surgicel* pack only	2
		Catgut mattress suture over Surgicel	4
Subcapsular haematoma (ruptured)	1	Catgut mattress suture only	1
Penetrating injury of the upper pole	1	Surgicel pack only	1
Multiple lacerations	5		
Mainly over the body	2	Catgut mattress suture over Surgicel	1
		Catgut mattress suture over Surgicel and omental wrapping of spleen	1
With shattered pole	3	Partial splenectomy only	1
		Partial splenectomy plus omental wrapping of spleen	1
		Ligation of torn polar vessel plus compression of spleen within a catgut ladder	1

* Surgicel*, Johnson and Johnson Ltd, UK

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bleeding is reported in only 8 (1·4 per cent). Two of these patients developed perisplenic haematomata 5–6 weeks after splenorrhaphy following institution of antiplatelet drug therapy for other reasons. In a further two cases a significant splenic tear had been missed at the original operation. In the remaining four cases, as in the case from the present series, the splenic injury was severe with multiple lacerations. However, there is no evidence that the need for a second laparotomy affected the eventual outcome in any of these cases. Nevertheless this small risk of rebleeding must be considered when deciding on the surgical management of a ruptured spleen.

Our experience has shown that splenic repair following trauma is feasible as a standard procedure in a district general hospital. It is generally safe and avoids a possibly unnecessary life-threatening risk of overwhelming infection. In 12 out of our 13 cases successful splenic repair was achieved (92 per cent) Other retrospective studies have recorded lower salvage rates, between 26 and 66 per cent[12,16,18–22,24,26] although, in other studies where a prospective policy of splenic conservation was followed[17,23,25], between 51 and 88 per cent of all ruptured spleens were saved This evidence suggests that splenic salvage may be possible in a greater proportion of cases than previously indicated. Nevertheless, one must be prepared to perform a total splenectomy when there is severe splenic damage especially if the case is complicated by other serious injuries and in retrospect our only unsuccessful case should have had total splenectomy on first exploration.

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Postoperative urinary retention in general surgical patients

A prospective study has been performed to measure the incidence of postoperative urinary retention in 280 general surgical patients. Eighteen patients (6 per cent) were catheterized after a range of operations under general anaesthesia. There was no statistical difference in the retention rate between men and women. Increasing age did not predispose to retention of urine. Of 72 patients who had either herniorrhaphy, haemorrhoidectomy or testicular operations, only 1 was catheterized, whereas 16 (23 per cent) of 70 patients undergoing laparotomy were catheterized. Most of these laparotomy patients had upper abdominal procedures carried out. Those having lower abdominal operations were usually catheterized pre-operatively and were excluded from the study. There was a significantly higher incidence of retention among patients who had long anaesthetics (>60 min). There was also a significantly higher incidence of retention among those who were ventilated, relaxed and reversed by atropine and neostigmine. Of those 193 patients who had opiate analgesia, 15 (8 per cent) developed retention of urine, compared with 3 (3 per cent) of the 87 patients who had non-opiate analgesia. There was a significantly higher retention rate among the patients who had opiate analgesia by intravenous infusion compared with those who had opiates by intramuscular bolus injection; 7 patients had painful and 11 had painless retention. This study suggests that postoperative retention of urine is a result more commonly of diminished awareness of bladder sensation, than of factors such as anxiety or local pain.

Keywords: Postoperative, urinary retention, general surgery patients

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Postoperative urinary retention is a recognized complication of any surgical operation, even in people with no pre-existing urinary symptoms. The patients most popularly considered to be at risk of developing retention are older men undergoing operations such as inguinal herniorrhaphy and haemorrhoidectomy which can be associated with local pain[1]. A single episode of retention can potentially cause serious morbidity to an individual. Overfilling of the bladder with subsequent overstretching and damage to detrusor muscle can potentially lead to motility problems or even atony, especially in the elderly[2]. Urethral catheterization itself carries the risk of trauma with its potential sequelae such as stricture formation, and the risk of infection which increases with every day that the catheter remains *in situ*[3,4]. In this study the incidence of postoperative urinary retention requiring catheterization has been studied in a group of general surgical patients.

Patients and methods

Two hundred and eighty consecutive patients undergoing a range of general surgical operations were studied. All the patients were under the care of three consultants. Patients who were catheterized pre-operatively were excluded, as were those who had known urinary symptoms and those taking medication which could affect bladder function. There were 182 male and 98 female patients. The mean age of the study group was 48·2 years (range 18–81 years). The operations performed on the patients are shown in *Table 1*. No operation involved instrumentation of the urinary tract. All the patients studied had a general anaesthetic. The duration of anaesthesia was measured from the time of induction to the end of skin closure. Induction was with thiopentone, and thereafter patients were maintained on halothane or ethrane and oxygen. One-third of the patients had fentanyl. A total of 167 patients were ventilated and therefore had suxamethonium or alloferin as a muscle relaxant, which was reversed by atropine and neostigmine at the end of the procedure. Postoperative analgesia was either opiate given as an intravenous infusion or as an intramuscular bolus injection, or alternatively, analgesia was non-opiate, given orally and in the case of dihydrocodeine was occasionally given intramuscularly (*Table 2*). For each individual a standard proforma was completed, recording past medical history, type of operation, anaesthetic technique and postoperative analgesia. In the event of urinary retention occurring, the proforma was completed by nursing staff recording the measures used to assist voiding, and by medical staff recording the type of catheter used if required, and eventually the duration of catheter drainage.

Urinary retention was noticed by patients in the case of painful retention and by medical or nursing staff in the case of painless retention, by observing the fluid balance chart or by palpating the lower abdomen.

Definition of urinary retention

We have defined retention as the inability to void urine for >12 h after induction of anaesthesia with >500 ml urine drained on catheterization. Retention was classified as being painful or painless.

Results

Of the 280 patients studied, 18 (6 per cent) developed postoperative retention and needed catheterization (*Table 1*). Seven patients had painful and eleven had painless retention. The mean volume of urine passed was 906 ml (range 580–1600 ml) for those with painful retention and 695 ml (range 520–900 ml) for those with painless retention.

Of the 182 men studied, 9 (5 per cent) developed retention of urine and of the 98 women studied 9 (9 per cent) developed retention of urine. The difference in retention rates between men and women was not statistically significant (χ^2 test, $0{\cdot}5 > P < 0{\cdot}1$). The mean age of men developing retention of urine was 50·2 years (range 18–78 years) and of women was

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Table 1 *Urinary retention rates after specific operations*

Operation performed	No. of patients	Initial difficulty passing urine (total)	Eventually able to void	Catheterized
Laparotomy	70	20	4	16
Inguinal herniorrhaphy	39	4	3	1
Haemorrhoidectomy	9	2	2	0
Appendicectomy	28	1	1	0
Testicular operations	24	1	1	0
Thyroidectomy	3	2	1	1
Mastectomy	3	0	0	0
Varicose vein surgery	54	0	0	0
Miscellaneous*	50	0	0	0

* Included circumcisions, ganglion removal, amputations, gynaecological procedures

Table 2 *Postoperative analgesia and urinary retention*

Analgesia	Patients without retention	Patients with painful retention	Patients with painless retention
Opiate IV infusion*	109	3	10
Opiate bolus†	84	1	1
Non-opiate‡	87	3	0

* Papaveretum, † morphine, papaveretum or pethidine, ‡ paracetamol, dihydrocodeine, mefenamic acid

49 years (range 21–81 years). The incidence of retention did not increase with increasing age.

A total of 30 patients (including those who were catheterized) experienced difficulty passing urine postoperatively (11 per cent), of these, 21 were men and 9 were women. Twelve of these patients (all men) eventually managed to pass urine with the help of simple measures, administered by nursing staff.

Type of operation

Patients having abdominal surgery had the highest incidence of retention. Of the 70 patients undergoing laparotomy, 16 (23 per cent) developed retention of urine. Of 39 patients who had an inguinal herniorrhaphy, 1 developed retention; and of 3 who had a thyroidectomy, 1 developed retention. Of the total of 72 patients undergoing either herniorrhaphy, haemorrhoidectomy, or testicular operations, 6 (8 per cent) had difficulty in passing urine and one was catheterized.

The 12 patients who had initial difficulty in voiding had the following procedures carried out laparotomy (4) herniorrhaphy (3), haemorrhoidectomy (2), appendicectomy (1), testicular surgery (1), thyroidectomy (1).

Duration and type of anaesthesia

Of the 280 patients, 196 patients (70 per cent) had an anaesthetic lasting for 60 or more minutes, while 84 patients (30 per cent) had an anaesthetic lasting for less than 60 min. Of those patients who had a long anaesthetic, 17 (9 per cent) were catheterized and of those who had a shorter anaesthetic, one was catheterized; this difference was highly significant ($\chi^2=6\cdot7$, $P<0\cdot05$) Of the 167 patients who were ventilated and given muscle relaxants, 24 (14 per cent) had difficulty passing urine and 16 (10 per cent) were catheterized Of the 113 patients who were not ventilated, 6 (5 per cent) had difficulty in passing urine and 2 were catheterized. There was a significantly higher incidence of retention ($\chi^2=6\cdot1$, $P<0\cdot05$) in the group of patients who had been ventilated and given muscle relaxants.

Type of postoperative analgesia

A total of 193 patients had opiate analgesia postoperatively (109 by intravenous infusion and 84 by bolus injection) and 87 patients had non-opiate analgesia (*Table 2*). Of the total number who had opiate analgesia, 15 (8 per cent) developed retention of urine. Of the 87 patients who had non-opiate analgesia, 3 (3 per cent) developed retention of urine. Of the 109 patients who had opiates by infusion, 13 (12 per cent) had retention and of the 84 who had opiate analgesia by bolus injection, 2 (2 per cent) developed retention of urine. The patients who had non-opiate analgesia represented a different operation group; none had had laparotomies. The patients who had opiate analgesia were given this as an intravenous infusion or by bolus injection, according to the personal preference of the doctor. Comparing these two groups, there was a significantly higher retention rate among the patients who had opiate analgesia by infusion ($\chi^2=6\cdot03$, $P<0\cdot05$).

Duration of retention

All the patients voided before admission to theatre. The mean time from induction of anaesthesia to recognition of retention was 17 h (range 3–26 h). This was slightly longer in the case of patients with painless retention (18·2 h) compared with those with painful retention (17·2 h), but this difference was not significant.

Duration of catheterization

For the 18 patients catheterized the mean duration of drainage was 3·2 days (range 12 h to 7 days). No patients were treated with an 'in/out' catheter. All except one patient passed urine without difficulty on removal of the catheter: the exception was a 72-year-old women who developed an atonic bladder requiring long-term catheterization, despite cholinergic therapy

Measures attempted to help a person void

A total of 30 patients (21 men and 9 women) had initial difficulty in passing urine postoperatively. the nursing staff intervened to help patients void in 21 (70 per cent); 9 patients (7 women and 2 men) were catheterized immediately that their retention was noticed The measures used to help voiding included giving oral analgesia in three cases, standing the patient up or walking in four cases, privacy in three cases, and sitting in a hot bath in five cases. Several different measures were tried with an individual patient in six cases. Helping measures were successful in helping 12 (57 per cent) patients (all male) to void, but were unsuccessful in 9 (43 per cent) patients. With female patients, helping measures were attempted in two but were not successful in either case; in seven women, helping measures were not tried. The seven women and two men who had no helping measures attempted had all had laparotomies.

Discussion

Micturition is a spinal reflex, influenced by higher brain centres and subject to voluntary control. The afferent limb of the reflex is mediated by pelvic splanchnic nerves from stretch receptors in the bladder wall. The efferent limb is via parasympathetic fibres running with the pelvic nerves. Impulses from stretch receptors in the bladder wall usually reach the sensory cortex when the bladder contains about 300 ml urine. The voiding reflex can then be facilitated by pontine centres or inhibited by midbrain centres[5].

If voiding is required, inhibition of the motor cortex is removed and the efferent parasympathetics produce detrusor contraction. As urine enters the posterior urethra, pudendal afferents produce inhibition of the tonic stimulation from anterior horn cells, the pelvic floor relaxes, levator ani descends and urine is voided.

Possible causes of painful retention in postoperative patients

If a patient experiences the urge to void, then the afferent limb of the micturition reflex is functioning. In painful retention, impulses from stretch receptors in the bladder are reaching higher brain centres, but the patient is unable to initiate voiding, perhaps because of immobilization by intravenous lines, nasogastric tubes or other equipment. Patients may also find it more difficult to void in a supine position, especially in unfamiliar surroundings without privacy. The problem may be exacerbated by a degree of mechanical outflow obstruction, in men with previously undiagnosed prostatic hypertrophy (although we found no higher incidence of retention in males). Local oedema or haematoma formation from a groin or perineal wound could also have the same effect.

Possible causes of painless retention in postoperative patients

In surgical patients the most probable reason for painless retention is that the sensory cortex is unaware of impulses reaching it from bladder stretch receptors. All 11 patients who had painless retention in this study had opiate analgesia, 10 of them by continuous infusion. The theoretical advantage of an infusion system is that patients have adequate doses of analgesia, constantly maintained. At adequate doses for a large wound, however, patients may well not feel discomfort from a distended bladder.

Without matching patients for sex and surface area it would be difficult to compare actual total doses of analgesia; however, 10 out of 11 patients with painless retention had infusions whereas only 3 out of 7 with painful retention had infusions It is likely, therefore, that those patients who were pain free received higher total doses than those who were still in pain.

Drug alteration of voiding function

The smooth muscle of the bladder and urethra contain cholinergic receptor sites; anticholinergic drugs such as atropine can therefore abolish or delay detrusor contraction[6,7]. Atropine has a plasma half-life of 2–4 h, or longer in elderly patients[8,9]. It is conceivable, therefore, that during its duration of action detrusor contractility would be diminished and that this would contribute to passive overfilling of the bladder.

In vitro studies on strips of detrusor have shown morphine encephalins to be potent pre-synaptic inhibitors of acetylcholine from post-ganglionic neurones[10]. Opiates would therefore lower the parasympathetic tone in the bladder and contribute to passive filling, in addition to their analgesic effects.

Other factors

Most patients had large volumes of urine in their bladders by the time that they were catheterized. It may be that in some cases retention could have been avoided if they had been encouraged to pass urine earlier. Clearly, in some cases it is not possible to intervene with simple measures in the early postoperative period, for example where patients have had a laparotomy and cannot stand or walk; these patients therefore need to be monitored regularly. We found that over 50 per cent of patients did pass urine with the help of simple measures. In several cases where it would have been feasible, measures were not attempted and a catheter was inserted immediately on discovering a retention. This happened most frequently with female patients

It is often assumed that postoperative retention is commonest in elderly male patients undergoing groin or perineal surgery. This study supports the idea that postoperative urinary retention is more often associated with diminished awareness of bladder sensation in patients after laparotomy.

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Parotid tumours: a review of parotid tumour surgery in the Northern Regional Health Authority of the United Kingdom 1978–1982

A review of inpatients treated for parotid tumours during the 5-year period 1978 to 1982 in the Northern Regional Health Authority of the United Kingdom revealed 376 new parotid tumours and 28 recurrent tumours. The incidence of new parotid tumours was 2·4 per 100 000 and of pleomorphic adenomas 1·5 per 100 000 per annum. Local excision was the most common operation and was employed to remove 156 (67·2 per cent) of the 232 pleomorphic adenomas but there was evidence of incomplete excision in 60 (38·5 per cent) of these tumours. Incomplete excision also occurred in 12 (15·8 per cent) of the 76 pleomorphic adenomas removed by conservative parotidectomy. Global temporary facial nerve palsy was more common after conservative parotidectomy for benign tumours (21·8 per cent) than after local excision (3·7 per cent) but global permanent nerve palsy only occurred after local excision (0·9 per cent). The widespread use of local excision resulted in its use in 12 (27·3 per cent) of the 44 malignant tumours. The low incidence of parotid tumours and their treatment by a relatively large number of surgeons resulted in limited experience for surgeons and few opportunities for training in parotid surgery.

Keywords: Parotid neoplasms, parotid gland surgery

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Parotid tumours are usually excised without a firm preoperative histological diagnosis for fear of dislocating tumour cells by open or needle biopsy, although some centres advocate and practise fine needle aspiration cytology[1]. The operation most frequently recommended is superficial or total conservative parotidectomy[2–4] but sporadic publications indicate that local excision or enucleation of pleomorphic adenomas followed by radiotherapy is an accepted procedure in many parts of the United Kingdom[5–7]. It is uncertain which operations are in predominant usage and the aim of this study was to assess the prevalence of different surgical practices in the Northern Regional Health Authority of the United Kingdom as well as their effectiveness in attaining complete tumour excision and avoiding facial nerve damage.

Patients and methods

Patients coded as suffering from benign or malignant parotid tumours for the years 1978–1982 in the Northern Regional Health Authority of the United Kingdom were identified and the clinicians involved in their treatment were contacted and asked for permission to review the case notes

The International Classification of Disease Index (ICD) 8th Revision Codes 142·0 and 210·2 were used with the additional codes of 230·0 and 235·0 from the 9th Revision

For the purpose of this study, seventh nerve palsy was regarded as global if it involved all or most of the facial muscles. Lesser degrees of palsy were classified as localized. If the palsy had persisted for more than 12 months it was classified as permanent. Excision was considered to be incomplete if the surgeon commented on capsular damage during the operation or the histopathological report indicated that excision was incomplete†

Results

The response from clinicians in the region was particularly co-operative and only one surgeon formally refused to take part in the survey. A total of 589 patients were coded as suffering from parotid tumours but 79 case notes (13·4 per cent) could not be traced, most commonly because of an incorrect hospital unit number. Case note review revealed that 106 patients coded as having parotid tumours had other unrelated conditions (false positives) but it also became apparent that patients with parotid tumours (sometimes identified from surgeons' personal records) were not always included in regional statistics (false negatives). It was possible to eliminate false positive cases by case note review but parotid tumours wrongly classified as a different disease could not usually be traced. This means that there is an underestimate of the number of parotid tumours treated although the incidence of tumours calculated from these data is higher than figures generally quoted for the United Kingdom[8].

Tumour incidence

During the years 1978–1982, the average population in the Northern Regional Health Authority was approximately 3·1 million. In all, 397 operations were performed for parotid tumours, of which 28 were for recurrent tumours. Seven tumours in debilitated patients unfit for operation had no histological diagnosis but the remaining tumours were classified as malignant tumours, pleomorphic adenomas and other benign tumours (mainly adenolymphomas and monomorphic adenomas) (*Figure 1*). The incidence of new parotid tumours was therefore 2·4 per 100 000 and of pleomorphic adenomas 1·5 per 100 000 per annum. The mean age of patients was 55·1 (range 16–95) years.

Surgical management of parotid tumours

Operations were classified as radical parotidectomy,

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†In practice, both criteria were fulfilled in 28 (33·3 per cent) of the 84 excisions classified as incomplete while 27 (32·1 per cent) were classified as incomplete on the basis of the operative record and 29 (34·5 per cent) on the basis of the histological report

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conservative parotidectomy or local excision; this last group includes local excision (sometimes with identification of a peripheral branch of the facial nerve), enucleations and rarely curettage. In some advanced tumours, a needle or open biopsy alone was performed.

Pleomorphic adenomas and other benign tumours

There were 232 patients (148 women and 84 men) with pleomorphic adenomas and 93 patients (38 women and 55 men) with other benign tumours (mainly adenolymphomas and monomorphic adenomas). The 232 patients with pleomorphic adenomas had a mean age of 49 (range 14–88) years. The 93 patients with other benign tumours had a mean age of 60·8 (range 27–91) years. *Table 1* shows the incidence of incomplete excision and of temporary or permanent facial nerve palsy following the different operations for pleomorphic adenoma and other benign tumours. Although the predominant operation was local excision (66·2 per cent) only 58 (37·2 per cent) of the 156 patients who had a local excision of a pleomorphic adenoma received postoperative radiotherapy.

Recurrent pleomorphic adenomas

There were 21 patients with recurrent pleomorphic adenomas; in 2 patients these followed conservative parotidectomy but in the remaining 19 the original operation was local excision with postoperative radiotherapy in 7 patients. The cumulative rate of global permanent facial nerve palsy was 23·8 per cent (five patients) and the median interval to the first recurrence of a pleomorphic adenoma was ten (range 2–34) years. Malignant change had occurred in five patients (23·8 per cent) between 19 and 39 years after the initial operation.

Malignant tumours

There were 44 patients (25 women and 19 men) with malignant tumours with a mean age of 72·4 (range 16–88) years. Twelve patients had a biopsy only; the death of five of these patients within 1 year confirmed the impression that a biopsy was usually performed for tumours that were advanced locally or distally or where the patient's general health was grave. Radical parotidectomy was performed in 7 patients, conservative parotidectomy in 13 patients and local excision in 12 patients. In at least 7 of the 12 patients who underwent local excision, the general fitness of the patients and the extent of the tumour did not seem to preclude a more radical operation.

Recurrent malignant tumours

This group does not include all patients with recurrent disease but only those who underwent inpatient surgery and presumably represents those patients where there was a problem with local rather than disseminated disease. Seven patients had operations for recurrent malignant tumours, and in five of these recurrence followed an original operation of local excision; notably two of these patients subsequently underwent conservative parotidectomy. The interval between the first and second operation ranged from 1 to 8 years with a median interval of 5 years.

Distribution of parotid tumours among surgeons

Figure 2 groups the number of surgeons according to the number of parotid tumours under their care during the 5-year period 1978–1982. Few surgeons had experience of more than two parotid tumours per annum. As a consequence 174 (43·8 per cent) of operations were performed by surgeons whose experience did not exceed an average of one parotid tumour per year. During the 5-year period, 13 surgeons in training appeared to play a major part either as an operator or assistant in 20 operations (7 conservative parotidectomies and 13 local excisions), i.e. 4 per annum.

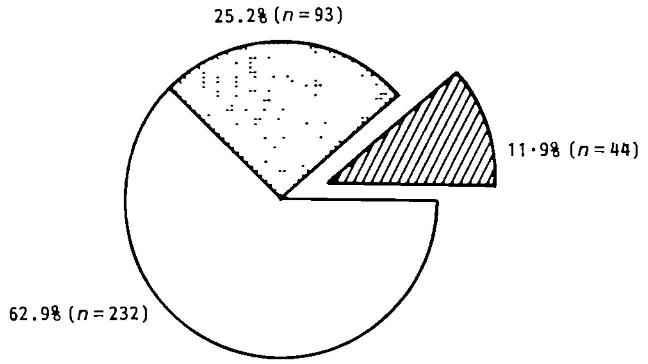

Figure 1 *Classification of 369 parotid tumours in the Northern Region Health Authority (1978–1982).* □, *Pleomorphic adenomas,* ▒, *benign tumours,* ▨, *malignant tumours*

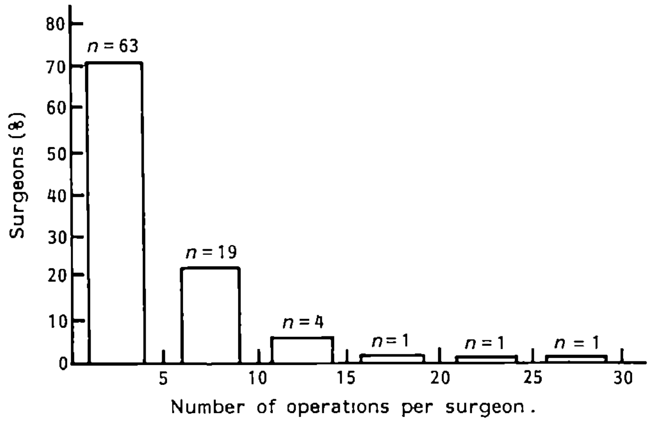

Figure 2 *Number of operations per surgeon for 89 surgeons in a 5-year period (1978–1982)*

Table 1 *Complications of surgery for pleomorphic adenomas and other benign tumours*

	Operations performed	Global temporary facial nerve palsy	Global permanent facial nerve palsy	Incomplete excision
Pleomorphic adenomas (n=232)	Local excisions 156 (67·2%)	4 (2·6%)	1 (0·6%)	60 (38·5%)*
	Conservative parotidectomy 76 (32 8%)	16 (21·0%)	0	12 (15·8%)*
Other benign tumours (n=93)	Local excisions 59 (63·4%)	4 (6·8%)	1 (1·7%)	11 (18 6%)
	Conservative parotidectomy 34 (36·6%)	8 (23·5%)	0	1 (2·9%)
All benign tumours (n=325)	Local excisions 215 (66·2%)	8 (3 7%)†	2 (0 9%)	71 (33 0%)
	Conservative parotidectomy 110 (33·8%)	24 (21 8%)†	0	13 (11 8%)

* There was a significant difference in the rate of incomplete excision, $P < 0\,01$; † There was a significant difference in the incidence of global temporary facial nerve palsy, $P < 0{\cdot}01$, P values obtained using χ^2 test with Yates' correction

Discussion

The incidence demonstrated in this survey of 2·4 parotid tumours and 1·5 pleomorphic adenomas per 100 000 population per annum is in excess of the figure quoted for the United Kingdom by Evans and Cruickshank of 1·1 per 100 000 for all salivary gland tumours excluding adenolymphomas[8]. These latter figures were based on Merseyside, North Wales and the Isle of Man but Lennox *et al.* found an exceptionally high incidence of parotid tumours in eastern Scotland of 4 per 100 000 (Reference 9) and it is uncertain whether or not the distribution of parotid tumours is heterogeneous throughout the United Kingdom. The total number of parotid tumours identified is certainly an underestimate because of problems already referred to regarding miscoding; it should be noted that Lennox *et al.*[9] found national statistics based on discharge diagnosis subject to errors as high as 20 per cent. However, the proportion of the different types of parotid tumour correlates well with those reported to the British Salivary Gland Tumour Panel[10] and, despite its shortcomings, this survey is thought to be representative both of the parotid tumours and of the practice of surgery in the Northern Regional Health Authority. As such, it reveals that the predominant operation for parotid tumours is local excision.

The employment of local excision for 156 (67·2 per cent) of the pleomorphic adenomas may be attributed to publications advocating this treatment combined with postoperative radiotherapy[5–7] but, surprisingly, 98 (62·8 per cent) of these patients did not receive radiotherapy. The high incidence of incomplete excision following these operations (38·5 per cent) gives cause for concern as recurrent pleomorphic adenomas have serious consequences; notably the high incidence of global permanent palsy following surgery for recurrent tumours and the similar rate of malignant change (23·8 per cent)—figures that correlate well with other publications[2,11]. Proponents of conservative parotidectomy[2–4] regard local excision as an inadequate operation but, nevertheless, when it is followed by radiotherapy, low rates of recurrence are reported[5–7]. Resolution of these differing views by means of a controlled prospective trial is unlikely because of the rarity of parotid tumours and the long interval to recurrent disease.

Unfortunately, conservative parotidectomy does not ensure complete excision of pleomorphic adenomas and the 15·8 per cent incidence of incomplete excision encountered in this survey is probably realistic. Donovan and Conley[12] found tumour extending to the margin of resection in 21 per cent of pleomorphic adenomas when they reviewed 100 lateral lobectomies and associated inadequate excision with tumours extending between the main trunk of the facial nerve into the fascia of the masseter muscle, tumours of the deep lobe or tumours near the zygoma. They nevertheless support conservative parotidectomy as an operation that, although it requires a more meticulous dissection, affords better exposure and is less likely to cause capsular damage. Although a high incidence of global temporary seventh nerve palsy followed conservative parotidectomy (21·8 per cent) this is a less serious consequence than global permanent palsy which only followed local excision.

Local excision has a more certain disadvantage if it results in incomplete excision of malignant tumours. Although radiotherapy is an important adjunctive treatment in the prevention of recurrent disease, particularly in large high grade tumours, the chances of curative treatment are best when surgical excision can encompass the primary tumour[13]. It is therefore important to obtain complete excision of small low grade tumours but unfortunately these are least likely to be recognized as malignant before operation and are therefore most at risk of inadequate excision. Twelve patients (27·3 per cent) had malignant tumours removed by local excision and at least seven of these tumours were suitable for a more radical operation. Pre-operative fine needle aspiration cytology may prove helpful in this respect, but it is not an established practice in the United Kingdom and may only result in an overall histological diagnostic accuracy rate of 74 per cent[13]. Any surgical approach to parotid tumours should be tempered by the knowledge that 12–26 per cent may be malignant[4,10,13].

The continued use of local excision means that it remains the preferred operation for many surgeons despite a high incidence of incomplete excision. It is likely that surgeons who operate on parotid tumours infrequently (most surgeons averaged less than one operation per year (*Figure 2*)) will favour local excision rather than the more testing operation of conservative parotidectomy, which may also be eschewed by those wishing to avoid global temporary facial nerve palsy. The surgeon's choice of operation is probably more dependent on the paucity of parotid tumours than previously acknowledged. Similarly the limited opportunities for surgical training demonstrated in this survey must have a profound effect on the practice of parotid surgery.

This survey encompasses a defined geographical region but may reasonably be assumed to reflect the practice of parotid surgery in, at least some, other parts of the United Kingdom. It demonstrates the problems and complications of surgical management which result in slight, but not negligible, risk to the facial nerve and, often, a failure to fulfil the aim of complete excision of parotid tumours.

Acknowledgements

It is a pleasure to acknowledge the cooperation of the surgeons, radiotherapists and other clinicians in the Northern Regional Health Authority. Our thanks are due to Mr J. Stevenson, Information Systems Section, the Department of Medical Statistics at the Regional Health Authority, for his help in identifying and tracing case notes, and also to the Medical Records Departments at hospitals throughout the Northern Regional Health Authority. We would like to thank Mrs Sandra Jordan for typing the manuscript. We are indebted to the Department of Audio-Visual Aids, The Medical School, Newcastle upon Tyne, for *Figures 1* and *2*.

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Correspondence

'The mammographic cancer'

Sir,

I read with interest the leading article on 'The Mammographic Cancer' (*Br J Surg* 1988, 75: 401) by Mr T S Boulter. This was a valuable and timely review of a subject that will be of increasing concern to all breast surgeons with the proposed increase in breast screening. Mr Boulter's guidelines to management are helpful but one point I feel needs clarification. He states that 'specimen radiology is mandatory and the wound is not closed until the films have been seen by the surgeon'. What action does he take if the specimen radiology does not confirm that the lesion in question has been removed? Presumably the marker used for identification of the lesion (a hooked needle for example) has been removed during the procedure and in the absence of on-table mammography what more can the surgeon do at this stage?

My own procedure having removed the segment of breast tissue in question, is to close the wound and return the patient to the ward awaiting a detailed radiological and pathological report. To date, I have with the aid of my radiological colleagues been able to excise correctly the lesion in question but accept that if missed at operation, a repeat attempt at localization at a later date may have to be done.

S. S. Miller

Aberdeen Royal Infirmary
Aberdeen
UK

Author's reply

Sir

I was glad to have the opportunity of seeing Mr Miller's letter and I thought I might briefly expand the message that I wish to give.

The reasons for localization biopsy are to produce histological explanation of impalpable masses and microcalcifications. There is a varying need for specimen radiology. It is mandatory in microcalcifications where there is often no visible or palpable abnormality in the specimen and yet where specimen X-ray is completely reliable. It is of less importance when the objective is a solid mass as here it is usual to find a palpable abnormality in the removed specimen and where an obvious small cancer, cyst or fibro-adenoma is removed then, of course, X-ray is not needed.

Finally, I think Mr Miller makes a good point for the use of contrast/dye injection techniques as the needle sometimes does get in the surgeon's way and when removed there is no longer the reference point of the coloured dye spot. That is why we go on using these techniques in our unit.

P. S. Boulter

Royal Surrey County Hospital
Guildford GU2 5XX
UK

Duodenogastric reflux measurement in Barrett's oesophagus

Sir,

I enjoyed the article by Gillen *et al.* on duodenogastric reflux measurement in Barrett's oesophagus (*Br J Surg* 1988; 75: 540–3) but I cannot accept their conclusion that bile acid reflux into the postprandial stomach is a feature of complicated Barrett's oesophagus but not of oesophagitis. Previous studies of intragastric bile acid concentration in oesophagitis have produced conflicting results. Collins certainly found no difference between postprandial intragastric bile acid concentrations between oesophagitis patients and controls, but this finding is at variance with the results reported by Crumplin. Since Collins in his study specifically excluded patients with complicated oesophagitis, it is not possible to use his data for comparison with Gillen's cases of complicated Barrett's. Mr Gillen needs to study a much larger group of patients with oesophagitis both with and without complications. This would provide very useful information concerning the significance of duodenogastric reflux in the aetiology of Barrett's oesophagus.

I. A. Eyre-Brook

Gloucester Royal Hospital
Gloucester
UK

Plain abdominal radiographs and acute abdominal pain

Sir,

I read with great interest Campbell and Gunn's article 'Plain abdominal radiographs and acute abdominal pain' (*Br J Surg* 1988, 75: 554–6). The appropriate use of diagnostic adjuncts such as radiographs is a controversial subject in both the UK and the USA. Certain aspects of determining the reliability of a particular test were not addressed by Drs Campbell and Gunn. Specifically, the true and false positive and negative rates were not reported. This information is needed to determine the sensitivity and specificity of a test.

A better way to determine the reliability of a test is by Bayesian analysis. This is a way to determine the probability of a disease being present given the positivity or negativity of a test. From their data, we see that the probability of a radiograph being positive for appendicitis given that the patient had appendicitis is 28·6 per cent. The probability of the test being positive given that the patient did not have appendicitis is 71·4 per cent. The authors did not present data to determine the rates of negative radiographs in patients with and without the disease. However, if we assume, as is generally accepted, that negative radiographs are totally unhelpful in the diagnosis of appendicitis, then the probability of a negative test in patients with and without the disease is 50 per cent. Furthermore, since the authors did not provide data on the rate of appendicitis in their population with abdominal pain, let us assume that the incidence of appendicitis in those patients suspected of having appendicitis is 80 per cent. (I use this figure since a negative laparotomy rate of 20 per cent for appendicitis is an acceptable standard of practice.) Therefore, the probability for a patient with suspected appendicitis and a positive radiograph is 61·6 per cent and with a negative radiograph is 80 per cent. From this we see that a patient with a positive radiograph is actually less likely to have appendicitis than one with a negative radiograph.

Campbell and Gunn have produced an excellent study of this problem. I agree with their conclusions concerning the lack of benefit of abdominal radiographs in the diagnosis of the acute abdomen. However, I feel that determining the reliability of a diagnostic test is best approached by Bayesian analysis.

V. Velanovich

San Francisco
California
USA

Author's reply

Sir,

We agree that the value of any test is best measured using specificity, sensitivity and Bayesian analysis. However, we are reporting the outcome of the arbitrarily selected usage of a test and not a definitive evaluation of the test itself. In order to apply Bayes' rule we would need data on prevalence, sensitivity and specificity, and this would require radiographic examination of all patients presenting with abdominal pain, whereas this test was performed on only 45 per cent of our patients. Thus although our numerators and denominators are inappropriate for the calculations suggested by Dr Velanovich the qualitative results should be relevant to everyday practice.

J. P. M. Campbell
A. A. Gunn

Bangour General Hospital
West Lothian EH52 6LR
UK

Epidural analgesia and postoperative insulin resistance

Sir,

I read with interest the paper by Uchida *et al.* (*Br J Surg* 1988, 75: 557–62) with regard to the effect of epidural analgesia on postoperative insulin resistance. We have also found both the glucose and insulin clamp techniques to be excellent methods for studying postoperative glucose metabolism. However, I was surprised by the minimal increase in rates of glucose disposal at higher insulin infusion rates. Certainly most previous authors using the insulin clamp technique have shown, at least, a threefold increase in glucose disposal with insulin infusion rates increasing from 1·2 to 10·0 milliunits kg^{-1} min^{-1} in normal subjects[1]

However, I would presume from the fact that some patients underwent total gastrectomy that a number of subjects had gastric cancer. As we have recently shown that such patients are insulin resistant[2,3], it would be interesting to know if these high-dose clamps were performed in cancer patients, thus explaining the low glucose disposal rates

The presence of malignancy can also have important consequences on the metabolic response to surgery Our own studies, performed admittedly at 48 h postoperatively, using the hyperglycaemic glucose clamp have shown patients with gastrointestinal malignancy to display worsening insulin resistance after surgery, which is further impaired if they are malnourished This occurred at a time when well nourished subjects with benign conditions have normal glucose disposal and insulin responsiveness[4] We would, therefore, suggest caution in the interpretation of postoperative studies, unless allowance is made for the effects of the primary pathology and nutritional status.

G. P. Copeland

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UK

1 Bergman RN *et al* Assessment of insulin sensitivity *in vivo*. *Endo Rev* 1985; **6** 45–86
2. Copeland GP, Leinster SJ, Hipkin L, Davis C. Glucose metabolism in patients with gastrointestinal malignancy but without excessive weight loss. *Eur J Surg Oncol* 1987, **13**: 11–16
3 Copeland GP, Leinster SJ, Hipkin L, Davis C Insulin resistance in patients with colorectal cancer. *Br J Surg* 1987; **74**. 1031–6
4 Copeland GP, Leinster SJ, Hipkin L, Davis C. Postoperative glucose metabolism in patients with gastrointestinal malignancy. *Eur J Surg Oncol* 1988; **14**: (in press)

Author's reply

Sir,

We thank Dr Copeland for his interesting comments on our paper In our patients, insulin infusion at rates of 1·2–5 0 milliunits kg^{-1} min^{-1} resulted in smaller increases of plasma insulin levels compared with the reported values[1–3]. Thus, glucose disposal values in our study were smaller than reported values, when comparing at the same insulin infusion rates We are unable to explain the smaller increase in insulin concentrations in our patients, but age or racial difference in insulin clearance may be causative factors The glucose disposal values at insulin concentrations of about 500–800 microunits ml^{-1} in our pre-operative patients were about 11–12 mg kg^{-1} min^{-1}. Those values are only slightly smaller than the values reported in other normal subjects[2,3].

In our 18 patients, 12 patients had gastric cancer and others had cholelithiasis, and each patient had different plasma insulin levels. Although insulin resistance in malignancy must exist, we could not unfortunately find evidence of a difference in glucose disposal between these two groups of patients of such limited numbers

I. Uchida

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Beppu
Japan

1 Rizza RA, Mandarino LJ, Gerich JE. Dose–response characteristics for effects of insulin on production and utilization of glucose in man. *Am J Physiol* 1981, **240** 30–9.
2 Kolterman OG, Gray RS, Griffin J *et al* Receptor and postreceptor defects contribute to the insulin resistance in noninsulin dependent diabetes mellitus *J Clin Invest* 1981, **68** 957–69
3 Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW Mechanisms of insulin resistance following injury *Ann Surg* 1982, **196**: 420–25.

Peritoneal encapsulation of the small bowel

Sir,

In their case report of peritoneal encapsulation of the small bowel Huddy and Bailey (*Br J Surg* 1988; **75** 262) state that this condition is not associated with malrotation This may not be the case

An 82-year-old man presented on 1 January 1988 with abdominal pain, vomiting and absolute constipation. His abdomen was distended and tender. X-rays of his abdomen revealed small bowel air–fluid levels At laparotomy, the entire small bowel, apart from the duodenojejunal flexure and the last 10 cm of ileum, was contained within a separate peritoneal sac The cause of his obstruction proved to be a constricting carcinoma of the caecum The bowel was malrotated The caecum lay in the right upper quadrant and, on opening the peritoneal sac, the terminal ileum emerged from behind the jejunum just distal to the duodenojejunal flexure, making subsequent right hemicolectomy somewhat more difficult.

Only nine other cases of peritoneal encapsulation of the small bowel have been reported and, of these, one was associated with a high caecum and partial volvulus suggesting some degree of malrotation[1] The aetiology of this condition is disputed[1,2] but appears to be related to events occurring as the midgut returns to the peritoneal cavity during the 12th week of intra-uterine life—the time when malrotation is initiated lending further support for an association of the two abnormalities. The condition is probably under-reported. The senior author has seen two cases in 4 years but as this was an incidental finding at laparotomy, it was not felt to warrant comment Since it is rarely associated with symptoms, the true incidence of this anomaly and of associated malrotation is unknown

T. N. Walsh
J. Russell

Mater Misericordiae Hospital
Dublin
Eire

1. Thorlaksen PHT, Monie IW, Thorlaksen TH. Anomalous peritoneal encapsulation of the small intestine· a report of three cases *Br J Surg* 1953, **40** 490–3
2. Estrada RL *Anomalies of Intestinal Rotation and Fixation* Springfield, Illinois. Charles C Thomas, 1958: 24–6.

Scoring systems in surgical practice

Sir

I found the leading article on scoring systems by Mr Schein in your August issue (*Br J Surg* 1988, **75**: 731) an excellent analysis I should like to draw attention to a further use of scoring systems in clinical practice which has been apparent in the therapy of burns for many years and has a parallel in the management of acute sepsis This is that scores define an approximate frontier of surgical survival which is there to be pushed back To know that a patient with an Apache II score of 40+ has a prior probability of death of 100 per cent is as much a challenge to achieve survival as it is a recipe for saying that all is inevitably lost I am concerned that there may be a growing tendency to use scores as a method of allowing a surgical team to throw in the towel rather than to perceive a challenge which requires them to be in the ring and battling for the survival of the patient

H. A. F. Dudley

Academic Surgical Unit
St. Mary's Hospital
London W2 1NY
UK

Perforated peptic ulcer management

Sir

The article by Keane *et al.* (*Br J Surg* 1988, **75**. 583–4) and the letter from Crofts (*Br J Surg* 1988, **75**· 619) ventilates what for us is an issue of considerable interest. For some 20 years the standard practice of one of the surgical units of this hospital has been to treat perforated peptic ulcer conservatively initially. We have adopted some of the general exclusion criteria proposed by Mr Keane, and we have been prepared to operate when conservative management fails With these reservations, we too have had a similar experience in that our results with this approach (120 patients) have matched, or bettered, those for immediate operative intervention

Our approach has been to re-assess patients 4–6 h after the onset of conservative measures, and operate then if there has not been any improvement. Our experience confirms that 75 per cent of ulcers will seal satisfactorily spontaneously.

We have also embarked upon a prospective trial involving all the surgical units, to see whether our previous unit *versus* unit experience would be borne out on a randomized basis, in our community

J. R. Cocks
J. McL. Dawson

Box Hill Hospital
Victoria 3128
Australia

Growth rate of colorectal liver metastases

Sir

Surely far too many assumptions are made in the paper on the growth rate of colorectal liver metastases by Finlay *et al.* (*Br J Surg* 1988, **75**. 641–4). They have assumed a single cell origin and both exponential and Gompertzian growth. Most worrying of all, however, is the extrapolation of the assumed growth curves to an assumed one cell origin These assumptions are based on values from 2 or 3 data points over a 1 year period

Few would argue about the existence of occult liver metastases in patients with colorectal cancer and many studies have clearly demonstrated their presence, however, to suggest that they may have been present for 2–3 years inevitably generates a degree of scepticism.

The heterogeneous nature of tumour cell kinetics in colorectal cancer is well recognized and it is likely that rapidly developing liver metastases occur from clones of malignant cells which disseminate widely and result in a poor prognosis with local and peritoneal recurrence Occult metastases could develop from malignant cells released from the primary cancer during its early malignant transformation, although they are likely to grow at a different rate from the primary tumour. In addition, whether metastases arise from single cells or clumps of micrometastases is open to a good deal of speculation

Nevertheless, if these findings are accurate the implications of such studies are that screening for colorectal cancer is unlikely to improve overall survival and that adjuvant therapy should be directed to the liver.

I. Taylor

University Surgical Unit
Southampton General Hospital
Southampton SO1 6HU
UK

An operation for incisional hernia

Sir

We read with interest the article by F. E Weale (*Br J Surg* 1988, 75 689) describing a technique for repair of incisional hernia. This is clearly based on a method of hernia repair first described by Boerema particularly for large incisional hernias[1]. The method newly described suffers from disadvantages not present in the original description. Boerema used subcutaneous Teflon® (Du Pont, UK) rods instead of Redivac® (O.E C. Ltd , UK) drain tubing, to which the sutures were attached, allowing complete closure of the skin, which is preferable to leaving four open discharging wounds with the risk of introducing infection It seems to be illogical to use soluble sutures as stronger and more durable material, such as monofilament nylon, allows the aponeurotic repair to consolidate for considerably longer (3–6 months). In Boerema's ingenious method the nylon sutures are looped around the first rod and tied through holes drilled through the second rod From 3 to 6 months after the repair both of the rods and the sutures are removed: a small incision is made over one end of the first rod, which is withdrawn; the second rod is similarly withdrawn removing all the suture material. Using this technique Boerema reported a failure rate of 5 in 40 cases followed up for a period of from 6 months to 2 years, 14 of these being recurrent incisional hernias

R. I. Hallan
R. W. Motson*

The London Hospital
London E1 1BB and
**Colchester General Hospital*
Colchester
Essex
UK

1 Boerema I Cause and repair of large incisional hernias *Surgery* 1971, **69**. 111–16

Author's reply

Sir

Your correspondents rightly note the omission of a reference to Boerema's paper which, with other material, was amended in response to editorial request. I welcome this fresh opportunity for crediting him with the call to overcome muscle retraction in the large incisional hernia, the key to treatment

In three preliminary cases I used buried tubing instead of Boerema's rods One became infected after a few weeks, so the tubes were removed early. Surprisingly the expected breakdown of the repair never materialized, but it seemed logical in future to utilize them as drains by exteriorization

His two rigid rods could not have contributed to patient comfort He was wrong to require prosthetic support beyond 4–6 weeks, and an additional second operation after 6 months. He had no way of telling when the rods should be extracted

The fear of introducing infection through drains is unfounded. Strong monofilament nylon should be avoided because of its liability to eventual sinus formation through scarred, and often thin, skin Realizing this, Boerema devised his method for removing it, slow absorption sutures not being available before 1971. The repair is full muscle thickness, not aponeurotic I have recently seen a patient whose repair is intact after 6 years

F. E. Weale

Gravesend and North Kent Hospital
Gravesend
Kent DA11 0DG
UK

Vitamin C after surgery

Sir

In his article, Dr Vallance (*Br J Surg* 1988, **75**: 366–70) provides evidence that the fall in buffy layer vitamin C following surgery is an artefact in the analytical procedure used However, he suggests that his findings would benefit from confirmation by measuring, after surgery, the vitamin C concentrations in the individual cell types that constitute the buffy layer To prevent unnecessary duplication of effort, may I draw attention to the fact that this work has already been done Dr Vallance's findings confirm our original work, where we showed reductions in buffy layer and plasma vitamin C of 43 and 36 per cent respectively on the first postoperative day. He is essentially correct in arguing that the buffy layer decrease is an artefact and is due to postoperative increases in polymorphonuclear cells, relatively low in vitamin C, diluting the platelet and mononuclear cell vitamin C contributions to the buffy layer. We calculated that 25 per cent of the buffy layer decrease was due to platelet dilution by leucocytes and 50 per cent was due to changes in the proportions of polymorphonuclear and mononuclear cells In contrast, the concentrations of vitamin C in the individual cell types that form the buffy layer (platelets, polymorphonuclear cells, mononuclear cells) change very little during the first 4 days following surgery. This chapter of vitamin C research can perhaps now be closed

C. J. Schorah

Department of Chemical Pathology
University of Leeds
Leeds LS2 9JT
UK

1. Schorah CJ, Habibzadeh N, Hancock M, King RFGJ. Changes in plasma and buffy layer vitamin C concentrations following major surgery. what do they reflect *Ann Clin Biochem* 1986; **23** 566–70.

Suture granuloma

Sir

We read with interest the recent article by Gleeson and McMullin (*Br J Surg* 1987, **74**. 1181), and would like to report a similar case

A thirty-one-year-old man was admitted to our unit with a 6-week history of upper abdominal pain, lethargy, a pyrexia and a 7 kg weight loss. His previous history included a left inguinal hernia repair and orchidopexy 4 months previously Physical examination revealed a large upper abdominal mass which appeared fixed and was non-pulsatile. Endoscopy in the first instance revealed only external compression of the stomach An ultrasound examination showed a normal liver, but a large 4 × 8 × 8 cm mass was seen lying adjacent to the fundus of the stomach. The radiologist thought that some of the features were those of a lymphoma A laparotomy was performed and a large mass involving the greater curve of the stomach, transverse colon, part of the small bowel mesentery and proximal jejunum .was found The appearances were those of a large malignant tumour This was resected *en bloc*, bowel continuity being restored Postoperatively he developed a small bowel obstruction for which a further laparotomy was necessary. An inflammatory mass was found to which the distal small bowel was adherent. This having been freed he made a slow but steady recovery.

Histology of the resected tumour mass showed an extensive stitch granuloma secondary to linen sutures.

An enquiry to the hospital where his hernia was repaired revealed that the hernial sac had contained omentum, part of which had been excised, haemostasis being secured with linen ties (We assume the omentum then retracted to the upper abdomen.)

Although stitch granulomas are known to occur, and linen has been blamed for the formation of stones in the biliary tree, we believe this to be the first case where a linen stitch granuloma has mimicked a large intra-abdominal malignancy, and required such radical surgery

D. C. Hunter
J. R. C. Logie

Department of Surgery
Raigmore Hospital
Inverness
UK

Tumour calcification after hepatic de-arterialization

Sir

The paper by Professor Bengmark on tumour calcification following hepatic de-arterialization in patients (*Br J Surg* 1988; **75**: 525–6) describes a new technique for repeated de-arterialization of the liver Tumour calcification occurred in all three patients treated in this way. The authors state that calcification of the hepatic metastases is a good prognostic sign although they do not quote any evidence in support of this. Instead, to substantiate this claim they quote a case report by Miller *et al.* which describes calcification of pseudomyxoma peritonei following intraperitoneal chemotherapy in a patient whose response to treatment is not stated Each of Professor Bengmark's three patients treated with de-arterialization also received intraperitoneal 5-fluorouracil so there is no evidence from this paper that de-arterialization plus intraperitoneal chemotherapy has any additional benefit over intraperitoneal chemotherapy alone. The authors state that in each patient there was regression of the tumour on CT scan although the CT scans illustrated clearly show an increase in size of tumour over a period of 5 months

Although this paper describes the technique of hepatic de-arterialization and demonstrates tumour calcification in three patients, there is no evidence that calcification indicates a response to treatment or that any patients have benefited from de-arterialization.

R. M. Charnley
D. L. Morris

University Hospital
Queen's Medical Centre
Nottingham NG7 2UH
UK

Recto-anal reflex after rectal excision

Sir

We disagree with Enriquez and Camuñas, and Keighley and Yoshioka (*Br J Surg* 1988; **75**: 621 (Correspondence)) that a long rectal muscle cuff is necessary for the preservation of the recto-anal reflex In our experience the recto-anal reflex was present in some patients after complete excision of the rectum with division of the muscle at the level of the pelvic floor[1,2]. We too have found that excision of the anal transitional zone does not appear to affect continence and agree with Keighley and Yoshioka that their findings cast doubt on the importance of the recto-anal reflex and the anal transitional zone in distinguishing flatus from stool

D. Z. Lubowski
D. W. King

The St. George Hospital
Sydney
Australia

1 King DW, Lubowski DZ, Talley NA, Pryor DS. Restorative proctocolectomy with ileal reservoir—a clinico-physiological study. *Aust NZ J Surg* 1987, **57** 555–8.

2 Nicholls RJ, Lubowski DZ, Donaldson DR. Comparison of colonic reservoir and straight colo-anal reconstruction following rectal excision. *Br J Surg* 1988; **75**: 318–20

Book reviews

There is a History in all Mens Lives

C. Illingworth. 145 × 210 mm Pp. 125. Illustrated Distributed by Tenovus-Scotland, Glasgow (a charitable trust for medical research in Scotland), 1988 £6 00.

Between the decades from the 1940s to the 1960s a remarkable phenomenon affected academic surgery in Scotland which has had repercussions to this day throughout Great Britain and many countries overseas and can be likened to the impact of Halsted on North American surgery It had its origins in three men, all with comparatively modest backgrounds and all of them combatant participants in World War I. The three were James Learmonth of Gatehouse of Fleet, William Wilson of Edinburgh and Charles Illingworth of Halifax in Yorkshire To the best of my knowledge they were between them responsible for producing 21 professors from their junior staff and indirectly responsible for creating many more in the next generation. Of the three, Sir Charles was by a short head the most prolific, creating what became widely and usually affectionately known as the 'Glasgow Mafia'. This group have gone on to add great lustre to British surgery and many of them are mentioned in the pages of this short but appealing biography

By his own admission, Sir Charles was not a high flyer at what he regards as an undistinguished school—Heath Grammar at Halifax. He left that institution during the first years of the War and eventually became a pilot in the Royal Flying Corps, being shot down behind enemy lines in the closing months of the War After his return he went, almost by accident, to Edinburgh University where he served some of the giants of the day, Wade and Wilkie in particular From there he progressed to the Regius Chair of Surgery in Glasgow where by his zeal, industry and ability he created what became one of, if not *the*, most influential departments in the country. Here in this little book is a delightful account of the years of struggle and success, it is full of deft and felicitous phrases which show that Sir Charles has lost none of the sharpness of mind which those of my generation recall so well For this reviewer, who pursued the same path from the same school (which I held in higher regard than Sir Charles) to the same university—though not thereafter to the heights achieved by the author—there is pleasant nostalgia in his description of both Yorkshire and Edinburgh life, and the author's clarity of recall shames my own fuzzy memories For a larger audience, the personal descriptions and vignettes, both from Edinburgh and Glasgow, will have an importance for future historians and make enjoyable reading, as does the author's personal description of his heart operation.

This book is an account—albeit highly selective—of a surgically and personally outstanding life. It is a pleasure to acknowledge his continued health and vigour His colleagues in the enterprise of academic surgery in Scotland will, from beyond the grave, salute him, though I would have welcomed a little recognition from him that he was part—perhaps the most important part—of a wider historical event

H. A. F. Dudley

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St Mary's Hospital Medical School
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Modern Surgery in Africa

D Pantanowitz. 170 × 242 mm Pp. 372. Illustrated 1988 Wynberg Sandton· Southern Book Publishers. 75 SA Rands.

On the outskirts of the rich white city of Johannesburg is a black township called Soweto Two million people live, love and fight there It is a dormitory town to supply black workers for the homes, the shops, the mills and the mines of its parent city Immediately outside the perimeter fence of Soweto is its one and only hospital, a phenomenon called Baragwanath. It was taken over from the British by the South African government in 1948 and now contains 2780 beds—the largest hospital in the southern hemisphere. It accepts patients not only from Soweto, but also from many of South Africa's neighbouring black countries.

Baragwanath is the largest of the five teaching hospitals of the medical faculty of the University of the Witwatersrand (which, like most South African universities, has a policy of no racial discrimination—a policy that brings it into conflict with the government from time to time). Serving the 500 or so surgical beds are 50 white and 23 black doctors. Half of the students are black, as are nearly all the nurses About 45 000 surgical patients attend as outpatients every year, and 15 000 are admitted The precise number is not known, owing to a remarkable deficiency in what is otherwise a technologically advanced hospital: there is no systematic audit of any kind. A few surgical units have introduced personal computers, but for the most part the storage and retrieval of data about patients is purely manual.

This is the background from which a splendid book has been produced It is called a textbook but it is far more than that Written by 47 surgeons and skilfully edited by Desmond Pantanowitz, the book is beautifully illustrated by line drawings and photographs, and the references are comprehensive, many being as up to date as 1987. There are four sections, these being trauma, vascular, general and miscellaneous

We tend to think of AIDS as the scourge of Africa, but there is no mention of it in Baragwanath, and it seems to be much less important than trauma. 'Approximately 10 000 people die on our roads each year, and about 30 000 lose their lives from assault'. The chapters on trauma are fascinating and, like the rest of the book, authoritative. Nowhere, however, can I find any reference to the rehabilitation of patients who have recovered, nor to the management of the disabled, nor indeed to long-term follow-up after admission for trauma or operations.

There are useful accounts of diseases that are rare in western countries These include not only idiopathic neurotrophic feet, Takayasu's arteritis, carotid body tumours and plunging ranulas, but also the extraordinary range of diseases caused by the ministrations of the traditional healers—for instance, battery acid enemas The chapters on appendicitis, ulcerative colitis and Crohn's disease are thoughtful and reveal our ignorance of the reasons for their rarity at Baragwanath compared with 'white' countries. Throughout the book there are also clear instructions on the management of diseases that are common all over the world.

This is an eminently practical book, well presented and interesting. It will remain on my shelves and I will often consult it

A. V. Pollock

Consultant Surgeon
Scarborough
UK

Acute pancreatitis

G. Glazer 180 × 238 mm. Pp. 440 Illustrated. 1988 London Baillière Tindall. £35.00

This is an excellent overview on the state of the art concerning acute pancreatitis The editors have won an impressive panel of experts including anatomists, pathologists, radiologists, internists and surgeons from the UK, the USA and one from Germany to report on all aspects of the disease, both experimental and clinical.

The book begins with a well-balanced analysis of the contentious issues in acute pancreatitis. Each of these controversies is then discussed in 16 well-illustrated and eminently readable articles. Each one begins with an illuminating historical introduction, thus putting the subject into perspective, and concludes with a complete and up-to-date list of references.

There are contributions on the anatomy of the pancreas (with all the numerous vascular and ductal variations), on the aetiology and pathology of pancreatitis as well as experimental models of the disease.

Three articles concern themselves with diagnostic assessment and prognostication The value of CT studies with contrast application is well documented here by convincing illustrations.

The final five chapters deal with treatment and here all the evidence is in favour of early non-operative management. Surgical intervention is reserved for the diagnosis of unclear cases (a rare event nowadays) and the management of complications, including protracted and recurrent pancreatitis

I would strongly recommend that anyone concerned with acute pancreatitis in the experimental laboratory, in the intensive care unit and in the operating theatre should buy this book

M. Trede

The Chairman
Department of Surgery
Mannheim
FRG

Notices and announcements

17–19 November 1988
Eighth Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information Mrs Marty May, Secretary to LTC Warren, F Bowland MD, Chief, Trauma Service, Department of Surgery, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

24–25 November 1988
Annual Meeting of the Vascular Surgery Society of Great Britain and Ireland
Leeds, UK
Information. Mrs P. D Huxtable, Flipper Pharmaceuticals Ltd., Harner House, High Street, West Drayton, Middlesex UB7 7QG, UK

25–26 November 1988
European Symposium on Ultrasonic Radiation Safety
Copenhagen, Denmark
Information Anne-Grethe Thorn, Secretary, Ultrasound Laboratory, Glostrup Hospital, DK 2600 Glostrup, Denmark

25–27 November 1988
22nd Annual Combined Surgical Meeting
Singapore
Information The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

28 November–2 December, 1988
Symposium and Workshop on Vascular Surgery
Singapore
Information The Secretariat, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0306

1–3 December 1988
American Back Society Fall Symposium on Back Pain
San Francisco, USA
Information American Back Society, 2647 E 14th Street, Suite 401, Oakland, California 94601, USA

8th December 1988
British Association of Surgical Oncology Forum: 'Head and Neck Cancer for the General Surgeon'
London, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

9 December 1988
Angioplasty: a Surgical or Radiological Procedure
London, UK
Information Janet Williamson, Secretary to Frank Ellis, 5 New Guy's House, Guy's Tower, London SE1 9RT, UK

9–10 December 1988
British Association of Surgical Oncology Forum: Winter Meeting
London, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–18 December 1988
Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons
Las Vegas, USA
Information Dr M R. Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988
Association of Surgeons of India Golden Jubilee Annual Conference
New Delhi, India
Information Dr N. C. Madan, Organizing Secretary 'ASICON-88', Room No 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

21–22 January 1989
Hong Kong Surgical Forum
University of Hong Kong, Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

12–18 February 1989
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London, UK
Information. Director, Courses Department, 65 Davies Street, London W1Y 2AA

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information Congress Secretariat, 7th Congress Ssian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

25–26 February 1989
Second Annual Congress on the North American Society of Phlebology
New Orleans, USA
Information Pat Curl, Course Coordinator, North American Society of Phlebology, 3960 Park Boulevard, Suite E, San Diego, California 92103, USA

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Surgical Masterclass for Consultants and Senior Registrars in General Surgery
Aviemore, UK
Information Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

12–15 March 1989
Current Problems in Breast Cancer
Vienna, Austria
Information: Secretariat ICS, Elisabeth Ribar Maurer, c/o Wiener Medizinische Akademie Alser Strasse 4, A 1090 Vienna, Austria

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information· The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–9 April 1989
4th ASEAN Otorhinolaryngological Head and Neck Congress
Singapore
Information Dr R E Stanley, Organizing Secretary, c/o ENT Department, Singapore General Hospital, Singapore 0316

12–14 April 1989
VIth International Conference: Polymers in Medicine and Surgery
Leeuwenhorst Congress Centre, The Netherlands
Information Joanna Evans-Thomas, Conference Officer, The Plastics and Rubber Institute, 11 Hobart Place, London SW1W 0HL, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
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6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

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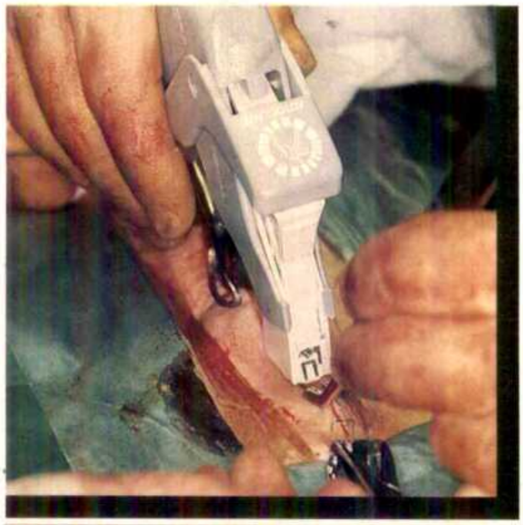

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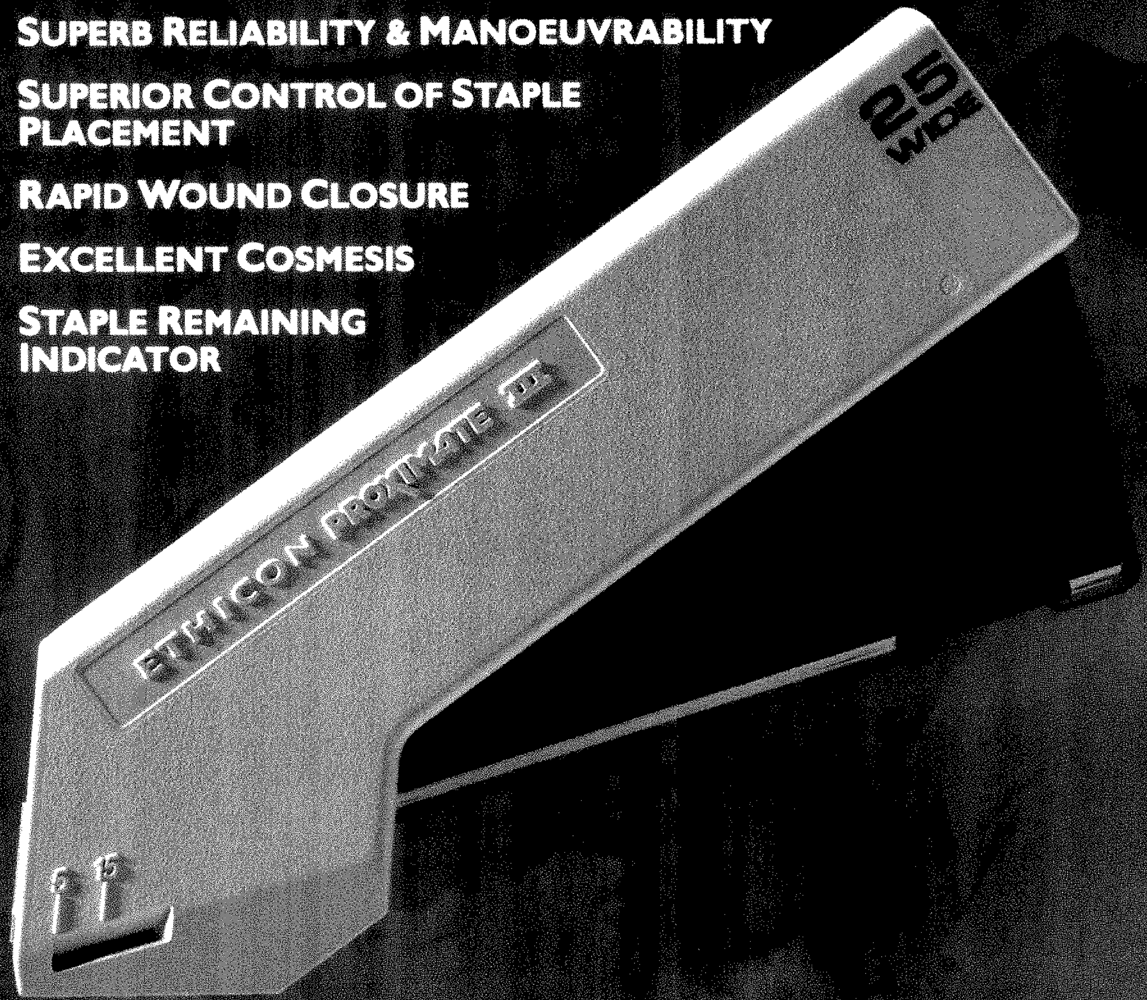

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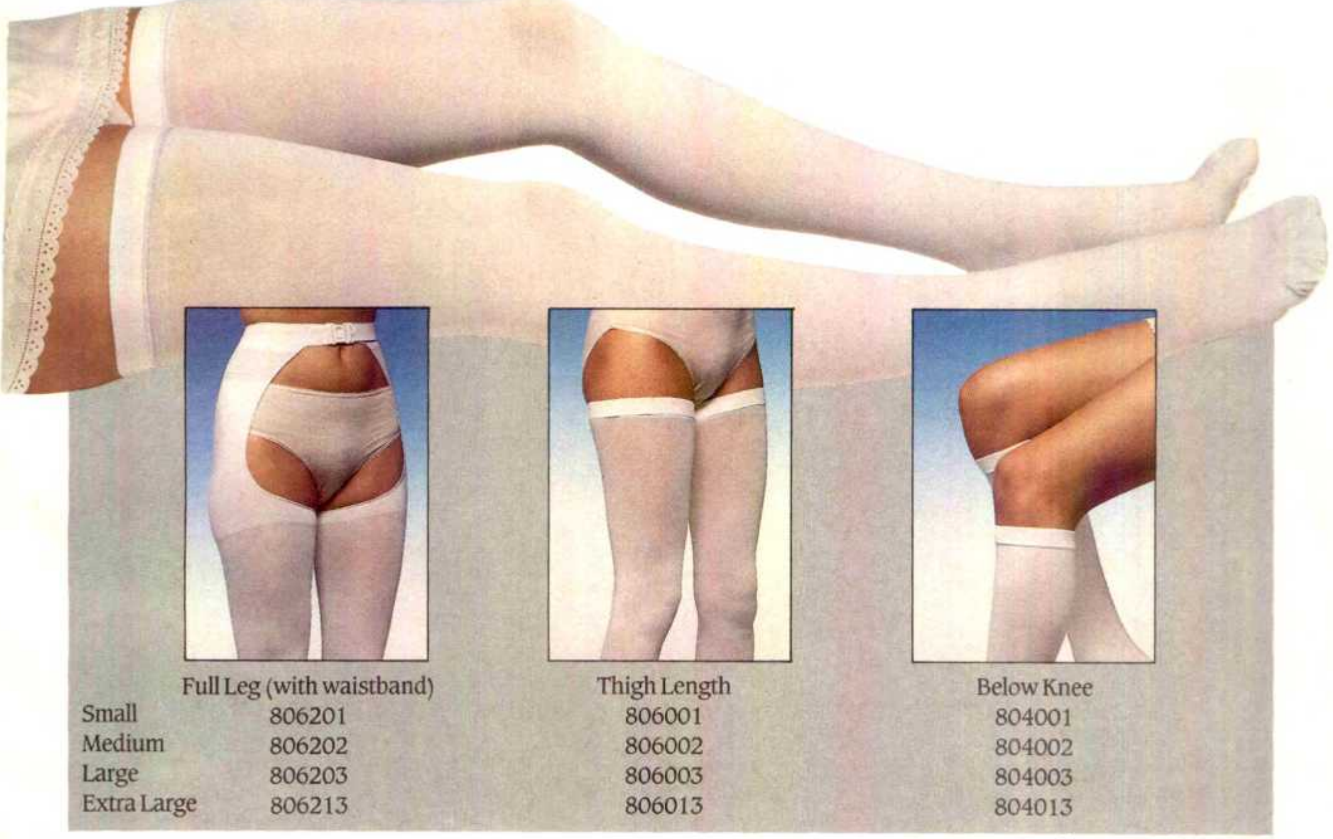

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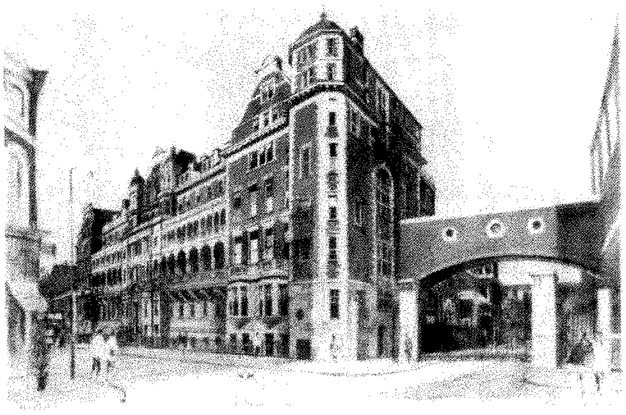

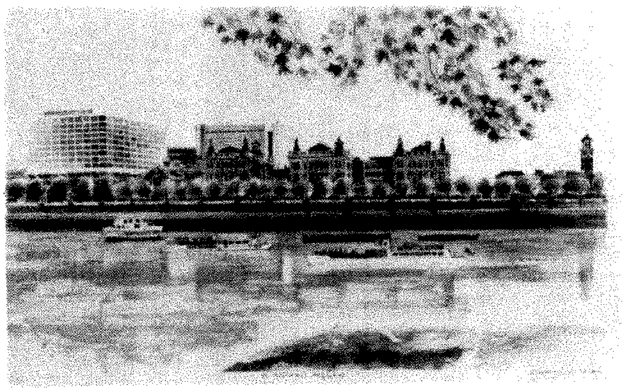

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Br. J. Surg. 1988, Vol. 75, December, 1153–1154

Postoperative abdominal sepsis

Postoperative sepsis is a preventable complication of abdominal surgery. For the individual surgeon it should be an infrequent event complicating less than 2 per cent of laparotomies[1,2] although related to the degree of operative contamination, ranging from 0·1 per cent of 'clean' to 6·5 per cent of 'dirty' cases[2]. The frequency can be much higher, however, particularly after contaminated and emergency procedures and it remains the single most important avoidable cause of morbidity and mortality after abdominal surgery. A retrospective study from Finland in this issue[3] reflects increasing interest in the aetiology, diagnosis and management of patients in whom the poor prognosis associated with postoperative intra-abdominal sepsis is compounded by organ failure.

When advanced age, malignant disease and debility coexist it is tempting to ascribe postoperative sepsis to such contributory but not necessarily causative factors and if postoperative organ failure aggravates a seemingly hopeless situation, therapeutic inaction may be justifiable. For many patients, however, vigorous treatment is not only justifiable but essential and the increasing number of publications reflects heightened contemporary interest. It is unlikely that there is any increase in the number of patients with sepsis but audit with more open discussion of surgical complications and changes in referral patterns contribute to the current interest.

In some patients, supportive therapy which prolongs survival without ultimate cure exposes the inadequacy of non-surgical management of postoperative sepsis and represents inefficient and expensive utilization of resources. Although supportive therapy contributes significantly to survival it is counter-productive if early signs of infection are treated empirically in preference to a rigorous search for the cause. Signs of sepsis, namely cardiovascular instability, deteriorating renal and respiratory function and gastrointestinal atony, show transient improvement but the progress of the disease process is only delayed if the underlying diagnosis is obscured. Access to intensive therapy and expert anaesthesia is mandatory when relaparotomy is required. The directness of early abdominal re-exploration lacks general appeal, with its implications of technical failure and not inconsiderable risks, but operation is essential not only when non-operative measures have failed but also to pre-empt organ failure.

Classification of postoperative abdominal sepsis is imprecise. Important differences relevant to management and outcome exist between a well-localized abscess and diffuse sepsis attributable to postoperative peritoneal contamination. In the former an abscess represents inadequate management of peritoneal contamination extant at the time of operation and if drained, often by the simple expedient of percutaneous drainage after radiological or ultrasonic visualization, it should resolve uneventfully. In contrast, sepsis secondary to peritoneal contamination as a result of either failure to eradicate a source of sepsis from the abdomen or leakage from a surgical suture line carries a more sinister prognosis. In the latter 'adequate drainage' is insufficient and continuing contamination of the peritoneum must be eliminated. This demands resection of the source of sepsis or dismantling of leaking anastomoses. More tentative manoeuvres, relying on diversionary proximal stomas and drains, are unreliable and the objective of treatment must be definitive control of sepsis.

All episodes of postoperative sepsis are not the result of technical failure or inadequate primary treatment but most probably are. In one large American series[4], when the sequelae of trauma were excluded, technical error was the commonest cause of intra-abdominal sepsis. In Europe where trauma is infrequent operative strategy and technique may be the most important factors. The onset of sepsis may be insidious but early diagnosis is possible in patients with anastomotic leakage if the possibility is recognized and acted on. Reluctance to entertain a diagnosis of technical failure is understandable but improvement in the prognosis of patients with intraperitoneal sepsis demands early diagnosis[5]. Delay resulting in organ failure complicating postoperative peritonitis is usually fatal[6], although some centres report a mortality rate of less than 25 per cent[7]. When there is suspicion of sepsis after an operation involving anastomosis, the integrity of the suture line must be established by contrast radiology. A negative investigation provides reassurance and a positive study permits rapid definitive management.

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While a proportion of patients survive without eradication of the source and a proportion in whom the source has been eliminated succumb, logic and indirect evidence favours the latter approach. Failure to control sepsis at the first operation leads to an accelerating process of deterioration which is difficult to reverse and increasingly heroic measures are required. The technical difficulties of re-exploration and the potential to compound the situation by damage to intact viscera are substantial and increase with delay and with each operation.

Ultraradical treatment with frequent relaparotomy in the absence of clinical indications, with the abdomen left open and with insertion of mesh or 'zippers' is a recent development. Convincing evidence of benefit to support more liberal use is lacking, with the possible exception of pancreatic sepsis in which eradication of the source is not practical[7,8]. We should heed the timely appeal from Finland for earlier diagnosis when management is relatively straightforward, before sepsis becomes established, and before the decline into multiple organ failure is irreversible.

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Br. J. Surg. 1988, Vol. 75, December, 1155–1156

Proximal cholangiocarcinomas

Altmeier in 1957 provided the first clear description of proximal cholangiocarcinomas. These small adenocarcinomas occurring at or near the hepatic duct bifurcation virtually all went undiagnosed before that time. Several years later Klatskin reported a large series of these lesions, and the tumour is widely known as the Klatskin tumour. For two decades after the description of this lesion most tumours remained undiagnosed. Patients presenting with jaundice were explored, often several times, only for the surgeon to be confronted with an apparently normal extrahepatic biliary tree, with a normal or collapsed gallbladder. Because of the inaccessibility and small size of most of these lesions, they are often not palpable or visible at laparotomy. Many patients were thought to have parenchymal disease when no obvious lesion was found at laparotomy, and the diagnosis, if made at all, was only confirmed at post-mortem examination. Today the diagnosis should be made promptly. The lesion should be suspected in any patient who presents with jaundice and who, on ultrasound or CT scan, has a dilated intrahepatic biliary tree with a normal extrahepatic biliary tract and a normal or collapsed gallbladder. The diagnosis can be easily confirmed by endoscopic retrograde or percutaneous transhepatic cholangiography. Therefore, a diagnosis which used to take weeks or months, and was often only made at post mortem, can now be made within 24 h of a patient presenting with obstructive jaundice.

Although the diagnostic workup has become standardized and routine, the management of these lesions remains variable and controversial[1]. Many of these lesions are potentially resectable, and it is the opinion of many that this should be the prime goal of therapy. However, since means to palliate such patients now exist which do not require laparotomy, the tumour should be staged so that only those with a likelihood of being resectable are subjected to operative intervention. To accomplish this, we believe that the patient needs to undergo two invasive procedures. First, the patient should have percutaneous transhepatic cholangiography rather than endoscopic retrograde cholangiography, because it is the anatomy proximal to the obstruction, rather than distal, that is important in staging. If on percutaneous cholangiography the tumour obviously extends up into secondary and tertiary biliary radicals in both lobes, the patient is not resectable and non-operative palliation should be considered. If the tumour does not appear to involve segmental branches, or involves segmental branches in only one lobe, the patient is potentially resectable. Next, all patients should undergo angiography. If the main hepatic artery is encased, the lesion is not resectable and laparotomy can be avoided. If the right or left hepatic artery is involved, the lesion still may be potentially resectable if lobectomy is added. On the venous phase, the portal vein can be identified and, again, if encasement is demonstrated, the lesion is not resectable. However, as with the artery, if only the right or left branch of the portal vein is involved, the lesion could still be resectable by adding hepatic lobectomy. Nuclear magnetic resonance might prove useful in the future, and may allow one to avoid angiography in staging. Hepatobiliary scanning plays no role in evaluation. If a patient is not deemed to be resectable, biliary obstruction can be relieved with percutaneously placed bilateral Ring catheters that are advanced past the tumour into the duodenum and then internalized. These can be converted to endoprostheses, or endoprostheses may at times be inserted by the endoscopic retrograde route. Many recommend radiotherapy for palliation, although there is no evidence for its efficacy.

If following cholangiography and angiography there is no clear evidence of unresectability, the patient should be explored. It is our preference at the time of percutaneous transhepatic cholangiography to pass Ring catheters down the right and left hepatic ducts, through the tumour, and into the distal biliary tree and duodenum[2,3]. Although this may require two or three trips to the diagnostic catheterization laboratory it is virtually always possible. These catheters are not placed for preoperative biliary decompression, as controlled trials have demonstrated their lack of efficacy in that context. However, they make resection of the tumour technically much easier and aid placement of Silastic® (Dow Corning) transhepatic biliary stents which I feel should be used routinely in reconstruction[4]. At the time of surgery, the distal biliary tree should be divided early, and the Ring catheters extracted from the distal common duct. Using them as a guide, the proximal biliary segment can be dissected, and the bifurcation easily identified. If the bifurcation can be resected without leaving gross tumour behind, this should be carried out. If tumour extends up into one lobe or the other, hepatic lobectomy can be added. At The Johns Hopkins Hospital, of 83 patients with proximal cholangiocarcinomas staged and explored, 33 (40 per cent) were resected for cure. In six, hepatic lobectomy was required. Once the lesion is resected, with or without hepatic lobectomy, the Ring catheters can be used to insert

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Silastic transhepatic biliary stents. Bilateral hepaticojejunostomies are then performed to a Roux-en-Y loop over the Silastic stents. Postoperatively the stents are left to drain dependently for 1 week until cholangiography demonstrates that there are no leaks. They are then internalized, with a view to leaving them in place permanently. They can be changed over guidewires every 3–4 months to avoid occlusion with sludge.

A number of alternatives are available if, at surgery, the lesion cannot be resected for cure. It is our preference still to go ahead and debulk the tumour by resecting the bifurcation if possible, and to reconstruct with bilateral hepaticojejunostomies over Silastic stents. In 13 of our 83 patients this procedure was performed. Others prefer a segment III bypass, or a modification of the Longmire procedure. Still others leave the tumour in place, but place transhepatic stents either as a U or J tube into a Roux-en-Y loop. The remaining 37 of our 83 patients were managed in this fashion.

Recently there has been renewed interest in total hepatectomy with liver transplantation[5]. The logistical problems are substantial since a graft has to be available well before one knows whether a potentially curable lesion is present, even with total hepatectomy. Currently this does not seem to be a likely solution to the many management problems that encumber proximal biliary tumours. Adjuvant therapy has been utilized in the form of intraoperative radiotherapy[6], external beam radiotherapy after resection, and internal radiotherapy using iridium-192 seeds. Although many surgeons are convinced of the efficacy of radiotherapy, there are no clinical trials to demonstrate its usefulness. Chemotherapy has been used only sporadically, and even though there are many small series demonstrating a 20 per cent response rate, there are no controlled data to demonstrate its value.

Whereas in the past most patients were dead within several months from unrelieved obstruction and secondary liver failure and/or cholangitis, many patients now survive for prolonged periods. We have one 10-year survivor, and two 5-year survivors, and more and more long-term survivors are being reported. Nevertheless, as with other gastrointestinal malignancies, overall prognosis is poor[1] and more effective adjuvant therapy is required. Although larger resections have been advocated, including resecting the portal vein, or even including pancreaticoduodenectomy with the hilar resection, it seems unlikely that extended resections will significantly improve long-term survival. Treatment failure and death are generally secondary to local recurrence, although at autopsy the tumour is usually widely disseminated. Appropriately delivered radiotherapy and effective chemotherapy will be needed to improve substantially the outlook for patients with this tumour. Perhaps we are at the same stage with proximal cholangiocarcinomas today that we were once with extremity sarcomas. Surgery, radiotherapy and chemotherapy were used two decades ago but, even following amputation, virtually everyone succumbed. Today, with smaller regional resections but with appropriate radiotherapy and chemotherapy, most patients survive. One of the difficulties with proximal cholangiocarcinomas is their rarity. In the USA probably fewer than 3000 patients with proximal biliary carcinomas are seen each year. This means that to have effective therapy regimens developed in prospective randomized trials, centralization of management will be necessary. This is already, in part, taking place as community surgeons have found these lesions particularly difficult to deal with. A co-operative prospective randomized trial has just begun at The Johns Hopkins Hospital and two other medical centres to evaluate the role of external beam radiotherapy, supplemented by internal radiotherapy with iridium-192, after curative or palliative resection for proximal cholangiocarcinomas. To our knowledge this will be the first prospective randomized trial of any form of treatment for this lesion. Centralization and many subsequent prospective randomized clinical trials will be required before substantial new progress is made in the management of proximal cholangiocarcinomas.

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Br. J. Surg. 1988, Vol. 75, December, 1157–1159

Relaparotomy for postoperative intra-abdominal sepsis in jaundiced patients

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During the period 1979–84, 30 abdominal re-explorations were performed for postoperative intra-abdominal sepsis and single or multiple organ failure in jaundiced patients. Postoperative sepsis was caused by intra-abdominal abscess in 16 cases (53 per cent), by suture line leakage in 9 cases (30 per cent) and by technical error in 5 cases (17 per cent). Abscesses occurred most commonly in the subphrenic space (6 cases), in the subhepatic space (6 cases) and in the lesser sac (5 cases). Sepsis was associated with single organ failure in 20 cases and with multiple organ failure in 10 cases. The overall mortality rate was 50 per cent (15/30). Factors that were statistically associated with fatal outcome were: serum bilirubin >100 μmol/l ($P < 0.008$), positive blood culture ($P < 0.013$), malignant disease ($P < 0.02$), multiple organ failure ($P < 0.02$) and age >60 years ($P < 0.031$). Mortality rose with the number of failed organs. Autopsy revealed continuing sepsis in 12 of the 15 fatal cases. Because mortality was high in spite of adequate operative drainage at relaparotomy, it is concluded that earlier definitive diagnostics are needed to lower the mortality rate.

Keywords: Intra-abdominal sepsis, reoperation

Intra-abdominal sepsis after abdominal surgery continues to be a dangerous and challenging major complication which considerably increases mortality. Although increased understanding of antibiotic therapy has lowered the mortality of intra-abdominal abscesses not associated with prior operation, little impact has been made on the results of repeated laparotomy for postoperative intra-abdominal sepsis[1]. While it is difficult to identify the need for re-exploration, and although the patients are high surgical risks, abdominal re-exploration often becomes mandatory. Severe intra-abdominal infection may lead to the development of single or multiple organ failure which makes the problem of sepsis considerably more difficult. The mortality rates of sepsis-induced multiple organ failure have been reported to be between 30 and 100 per cent[2–4].

The present study is a retrospective analysis of 30 consecutive jaundiced patients who required laparotomy for postoperative intra-abdominal sepsis at the Oulu University Central Hospital, Finland.

Patients and methods

A total of 1622 patients were treated at the surgical emergency unit of the Oulu University Central Hospital between January 1979 and December 1984. We reviewed the hospital records of all jaundiced patients (124 patients) to identify those who had undergone re-exploration for postoperative intra-abdominal sepsis and developing organ failure. The 30 patients so identified all underwent reoperation in the hope of reversing this organ failure. Burn patients, obstetric patients, multiple trauma patients as well as those undergoing reoperation for wound dehiscence were excluded. The 30 cases were analysed retrospectively with a complete review of hospital and autopsy records, laboratory studies, operative notes and bacteriological cultures The reports of primary operations were specifically examined to detect any technical error which might have predicted the need for re-exploration. The types of primary operation are listed in *Table 1*

Among the 30 reoperated patients the male female ratio was 16:14. The median age was 60 years with a range of 33–83 At reoperation, the presence of peritonitis or a localized abscess was regarded as an intra-abdominal infection and the diagnosis was confirmed by at least three of the following features· (1) positive blood culture, (2) positive bacterial culture from the purulent exudate of the abdomen, (3) fever >38 0°C, (4) elevated white cell count (over 12 000 cells/ml[3]). An abscess was deemed present if there was gross evidence of walled-off pus

The criteria for determining organ failure were as follows. (1) liver: jaundice with serum bilirubin level >50 μmol/l (normal 2–20 μmol/l), serum glutamic oxaloacetic transaminase (SGOT) level >80 units/l (normal <40 units/l), (2) kidney. serum creatinine >150 μmol/l (normal 60–115 μmol/l), oliguria or hyperkalaemia persisting for 48 h despite adequate volume resuscitation, (3) lung: need for ventilatory support

Gallstones were the most common underlying disease leading to sepsis (*Table 2*). None of the patients had intra-abdominal sepsis before primary surgery. Eleven patients received some form of antibiotic prophylaxis before primary surgery and 11 patients also received total parenteral nutrition after reoperation Surgical management at reoperation was divided into drainage procedures (16 cases) and specific operative procedures (14 cases). The specific operative procedure was chosen according to the operative findings and six bile duct reoperations, six enterostomies and two intestinal resections were performed. Classification into the category of malignant disease was based on the operative finding of malignancy which was histologically confirmed Operative mortality was regarded as death occurring within 30 days of reoperation or as a consequence of a continuing septic process unresolved at the secondary operation.

The factors tested with regard to their involvement with fatal outcome were positive blood culture, malignant disease, multiple organ failure, age >60 years, diffuse peritonitis, Gram-negative infection, multiple species infection, specific operative procedure, high serum

Table 1 *Primary operative procedures performed in the 30 patients*

Procedure	No
Cholecystectomy	10*
Subtotal pancreatectomy	7
Total gastrectomy	3
Biliary bypass	3
Whipple procedure	2
Gastric resection	2
Exploratory laparotomy	1
Hepatic resection	1
Intestinal resection	1

* Of the 10 patients, 7 also underwent choledochotomy

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Table 2 *Underlying diseases in the 30 patients*

Disease	No.
Gallstones	9
Pancreatitis	7*
Pancreatic cancer	5
Gastric cancer	3
Hodgkin's lymphoma	1
Cancer of the common bile duct	1
Intestinal obstruction	1
Gastric ulcer	1
Duodenal ulcer	1
Haemangioma of the liver	1

* Four patients had gallstones, in three cases pancreatitis was caused by alcohol

Table 3 *Causes of intra-abdominal infection in the 30 patients*

		Mortality	
Cause	No.	No.	%
Abscess	16	7	44
Leakage	9	5	56
Technical error	5*	3	60
Total	30	15	50

* Technical error caused two intra-abdominal abscesses

bilirubin and SGOT values. The statistical significance of these clinical variables was determined by χ^2 analysis (contingency table method). P values of $<0{\cdot}05$ were considered significant

To determine the significance of elevated serum bilirubin and SGOT values the patients were divided into the following subgroups: patients with serum bilirubin values $\leqslant 100\,\mu$mol/l ($n=11$) and $>100\,\mu$mol/l ($n=19$); and patients with SGOT values $\leqslant 100$ units/l ($n=15$) and >100 units/l ($n=15$)

Results

Of the 1622 patients dealt with by the surgical emergency unit, 30 (1·8 per cent) were re-explored because of intra-abdominal sepsis in the study period. The majority (19 of 30) of these re-explorations were performed on the basis of clinical findings only. Computed tomography and ultrasonography aided the diagnosis in eight patients and radiographic contrast studies were useful in the remaining three patients. Positive blood cultures were documented pre-operatively in eight patients; *Escherichia coli* (3 cases), *Klebsiella pneumoniae* (2 cases) and *Enterobacter* (2 cases) were the organisms most often cultured.

Of the 30 patients, 15 died despite operative treatment. The mortality rates of those who received antibiotic prophylaxis (45 per cent) and of those who received total parenteral nutrition after reoperation (64 per cent) were not statistically different from the mortality rate of the other patients.

The mean time interval between the first and second operation was 14 ± 8 days and this did not differ between the survivors (14 ± 9 days) and non-survivors (13 ± 6 days). The type of primary operation did not have a significant effect on mortality The causes of intra-abdominal sepsis are detailed in *Table 3*. The most common conditions identified at re-exploration were abscess (53 per cent) and suture line leakage (30 per cent). Of the abscesses, five developed in patients who had undergone operation for haemorrhagic pancreatitis, four followed various types of cancer operation, one developed after suture of a perforated gastric ulcer, two were postoperative infections of unknown origin and four were after operations for gallstones. The location of the abscess had no significant influence on mortality (*Table 4*).

Leaking anastomosis accounted for 30 per cent of the intra-abdominal infections In five cases a biliary–enteric, in three cases an oesophagojejunal, and in one case an entero-enteric anastomosis had leaked. Two patients died after biliary–enteric leakage, two patients died after oesophagojejunal leakage and the patient with entero-enteric leakage also died. The five recognized technical errors included two cases of biliary peritonitis following a dislodged T tube, two cases with unrecognized peroperative perforation of the intestine at the first operation and one case with accidental ligation of the common bile duct. The patient with common bile duct ligation and one of the patients with perforated bowel later succumbed.

Five patients underwent multiple relaparotomies. Three patients operated on for recurrent or persistent abscess recovered. The two deaths in this group included a patient with a lesser sac abscess caused by haemorrhagic pancreatitis and a patient with leakage from an oesophagojejunal anastomosis after total gastrectomy performed for gastric cancer.

The frequency of organ system failure and the associated mortality are listed in *Table 5*. Failure of more than one organ system increased mortality but the differences did not reach statistical significance. Failure of two and three organ systems was followed by a mortality rate of 75 per cent and 100 per cent, respectively.

The factors for predicting outcome are presented in *Table 6* The factors that statistically correlated with increased mortality included serum bilirubin $>100\,\mu$mol/l, positive blood culture, malignant disease, multiple organ failure and age >60 years. The other variables, Gram-negative or Gram-positive infection, multiple or single species infection, diffuse peritonitis or localized abscess, abscess drainage or specific operative procedure and SGOT concentration $\leqslant 100$ or >100 units/l were not associated with statistically significant differences in mortality. The fatality rates of the patients with Gram-positive or Gram-negative infection were 25 and 54 per cent respectively, those of the patients with single or multiple species infection were 55 and 47 per cent respectively, those of the patients with localized abscess or diffuse peritonitis were 39 and 67 per cent respectively, and those of the patients with SGOT $\leqslant 100$ and >100 units/l were 53 and 47 per cent respectively. Both abscess drainage and specific operative procedures were followed by a 50 per cent mortality rate.

The median age of the survivors (55 years) was less than that of the non-survivors (60 years) but the difference was not significant Of the 15 non-survivors, 8 suffered multiple organ

Table 4 *Location of intra-abdominal abscesses*

		Mortality	
Abscess	No	No.	%
Subphrenic	6	3	50
Subhepatic	6	1	17
Lesser sac	5	2	40
Pelvic space	1	1	

The differences were not statistically significant

Table 5 *The influence of organ-system failures on mortality*

		Mortality	
	No.	No	%
Failed organ system			
Liver	30	15	50
Kidney	9	7	78
Lung	3	2	67
Number of organs with failure			
1	20	7	35
2	8	6	75
3	2	2	100

Table 6 *The relationship between various pre-operative predictors and mortality*

Predictor	No	Mortality No.	Mortality %	*P*
Serum bilirubin >100 μmol/l	19	13	68	0·008
Positive blood culture	8	7	88	0·013
Malignant disease	10	8	80	0·020
Multiple organ failure	10	8	80	0·020
Age >60 years	16	10	63	0·031
Diffuse peritonitis	12	8	67	n.s
Gram-negative infection	26	14	54	n.s
Specific operative procedure	14	7	50	n s.
Multiple species infection	19	9	47	n s
SGOT >100 units/l	15	7	47	n.s.

n s, Not significant; SGOT, serum glutamic oxaloacetic transaminase

failure compared with only 2 of the 15 survivors ($P < 0{\cdot}02$). The survivors suffered failure of an average of 1·2 organs and the non-survivors of 1·6 organs. The location of abscesses, the number of emergency operations and the number of explorations did not differ between these two groups. In 12 of the 15 patients who died, autopsy revealed ongoing intra-abdominal sepsis. In three cases the intra-abdominal situation had resolved after the second operation before these patients succumbed. All of these 15 patients had undergone adequate intra-abdominal exploration for the source of infection, and the drainage of the infected focus can be regarded as having been effective.

Discussion

Improvements in critical care medicine have increased immediate survival rates after severe abdominal injury or disease states, but this increase has paradoxically increased the incidence of postoperative infections that may ultimately contribute to complications and death[5]. It may be that relaparotomy is used at present in patients who previously would not have tolerated it. Because of difficulties in obtaining early diagnosis of postoperative intra-abdominal sepsis, planned relaparotomy to obviate diagnostic delay has been recommended[6]. On the other hand, multiple organ failure carries such a grim prognosis that it has been advocated as a valid indication for abdominal exploration[7]. Our data lead to the conclusion that relaparotomy is usually undertaken at a stage when multiple organ failure has already supervened.

The overall mortality rate in the present series was 50 per cent. If one organ had failed, the mortality was 40 per cent but failure of two or three organs was associated with mortality rates of 63 per cent and 100 per cent, respectively. This rate is slightly more than noted by Fry *et al.* in a series of patients with intra-abdominal abscesses[8]. They determined that single organ failure was associated with a 23 per cent mortality rate, two organ failure with a 53 per cent mortality rate and three organ failure with a 79 per cent mortality rate. Pine *et al.*[9] prospectively examined factors predicting mortality in patients with intra-abdominal sepsis and observed a 10 per cent mortality rate with single organ failure, a 50 per cent mortality rate with two organ failure and a 100 per cent mortality rate with three organ failure. Hinsdale and Jaffe[10] recently reviewed 87 abdominal re-explorations for intra-abdominal abscesses. The overall mortality rate in their series was 43 per cent but the mortality rate for patients explored only on the basis of multiple organ failure was 81 per cent.

Although it has been suggested that a group of non-bacteraemic intensive care patients exist who are identical with regard to clinical parameters and course to patients with proven bacteraemic sepsis[11], patients with a positive blood culture in our series experienced a significantly higher mortality rate than those with negative blood culture. This finding is in agreement with that of deVillota *et al.*[12]. In patients with intra-abdominal sepsis, old age is a predictor of mortality[1,8,9,10]. Malignant disease can cause malnutrition, protein depletion, energy deficit, altered host defence mechanisms and predisposition to infection, which makes the poorer outcome of these patients understandable. In this series there was a clear, although not statistically significant, increase in mortality rate among the patients operated on for diffuse peritonitis and also among those with Gram-negative infection. This is in agreement with the findings of others[13,14,15].

Relaparotomy reversed multiple organ failure in a relatively small proportion of patients with postoperative intra-abdominal sepsis in the present series in spite of adequate drainage However, there are patients who survive reoperation, and re-exploration must still be regarded as indicated. It has been suggested previously that early diagnosis and treatment of intra-abdominal abscesses are the most important factors in improving survival[16]. We agree with this and take the view that early monitoring of high risk patients with modern diagnostic methods and laboratory tests could lead to an earlier discovery of septic foci and to earlier operative drainage of the infected focus. In this way, the impending multiple organ failure could possibly be prevented in some cases and the mortality of these seriously ill patients reduced. For earlier diagnosis, we intend to evaluate the worth of acute-phase reactant proteins in the recognition of the postoperative infective states and in monitoring the course of infection.

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Calmodulin antagonist trifluoperazine inhibits polyamine biosynthesis and liver regeneration

Polyamines are essential for cell growth and differentiation. Trifluoperazine (TFP) is a potent, competitive inhibitor of the calcium–calmodulin complex. TFP, when given to rats after partial hepatectomy, causes a significant decrease in DNA synthesis. The purpose of this study was to examine the effects of TFP on polyamine biosynthesis and on liver regeneration after partial hepatectomy. TFP (60 mg/kg, bodyweight) or saline control was administered to 80 male Sprague-Dawley rats 2 h before, 2 h after, or at the time of hepatectomy. Polyamines (putrescine, spermidine and spermine) were measured at the time of hepatectomy, and at 6, 24, 48, and 72 h after hepatectomy. TFP, when it was administered either 2 h before or at time of hepatectomy, blocked increases in putrescine that are seen normally at 6 h after hepatectomy. When TFP was given at the time of partial hepatectomy, putrescine was increased at 24 h, and then returned to normal levels at 72 h. Spermidine was inhibited at 24 h, but not at 48 and 72 h. Spermine was not significantly altered at any time. The administration of TFP 2 h after hepatectomy did not significantly alter concentrations of polyamines. The weight of regenerating liver was decreased by TFP at 48 h (23 per cent) and 72 h (22 per cent) after hepatectomy. These findings provide evidence that the calcium–calmodulin complex is required for the synthesis of liver polyamines before liver regeneration can proceed.

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The polyamines putrescine, spermidine and spermine occur in almost all animal and plant tissues that have been examined, and they have been shown to play vital roles in cell growth and differentiation[1–4]. The initial and rate-limiting step in the pathway of polyamine synthesis is the decarboxylation of ornithine by ornithine decarboxylase (ODC). ODC values are increased in both stimulated cultured hepatoma cells[5], as well as after partial hepatectomy[6,7]. ODC has been shown repeatedly to be necessary for DNA synthesis[8–14]. Luk[15] demonstrated that after partial hepatectomy increases in both ODC activity and polyamine content of liver tissue are essential for DNA and protein synthesis and tissue proliferation during liver regeneration

Calmodulin, a calcium receptor protein, appears to mediate many calcium-dependent processes such as contraction, secretion, and nerve function[16], and may also participate in the control of cellular proliferation[17] *In vitro* studies have shown that calmodulin influenced the disassembly of microtubules in a calcium-dependent manner[18], and stimulated DNA synthesis in rat liver cells[19]. Antibodies against calmodulin have shown an association between this calmodulin and the assembly or disassembly mechanism of the mitotic spindle[20], which suggests that calmodulin may play a role in mitosis. Elevations in the intracellular concentrations of calmodulin have been found in cells undergoing malignant transformation[20,21], which raises questions regarding the mechanism of action of calmodulin in the process of cellular proliferation or transformation[22].

The purpose of our study was to examine the effects of trifluoperazine, a potent competitive inhibitor of calmodulin, on polyamine biosynthesis during liver regeneration.

Materials and methods

Drugs

Trifluoperazine dihydrochloride (TFP) was purchased from Sigma Chemical Company (St Louis, Missouri, USA).

Animals

Adult male Sprague-Dawley rats were purchased from Harlan Sprague-Dawley (Indianapolis, Indiana, USA) They were allowed *ad libitum* access to water and standard rat chow (Formulab 5008, Ralston Purina Company, St. Louis). They were fasted 24 h before and 24 h after surgery. Partial hepatectomy (68 per cent) was performed, utilizing light ether anaesthesia, between 09.00 h and 12.00 noon[23] The entire resected portion of liver was immediately weighed and snap frozen in liquid nitrogen. The remaining portion of the liver was removed at reoperation at either 6, 24, 48, or 72 h after the original resection, and was snap frozen in liquid nitrogen and stored at −70°C until assayed for polyamines

Polyamines

Samples of liver for measurement of polyamines were homogenized in 2 ml of 4 per cent sulphosalicylic acid per gram of liver weight, and were then allowed to remain on ice for 30 min The homogenate was centrifuged at 10 000 r.p.m. for 5 min The polyamine content of the supernatant was analysed using a Dionex 2110-i high pressure ion chromatography unit (Dionex Corporation, Sunnyvale, California, USA). Polyamines were eluted using a potassium buffer system[24]

Statistical analysis

Statistical significance was calculated using the Student's t test for independent populations. Significance was set at $P < 0.05$. The data are presented as mean ± s.e.m.

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Table 1 *Effect of trifluoperazine on polyamine concentrations at time of hepatectomy and at 6 h post-hepatectomy, when trifluoperazine dihydrochloride was given 2 h before, at the time of, or 2 h after hepatectomy*

	Time of drug administration					
	2 h before partial Hx		At partial Hx		2 h after partial Hx	
	Time of Hx	6 h	Time of Hx	6 h	Time of Hx	6 h
Putrescine						
Control	46 ± 7	588 ± 244	12 ± 2	496 ± 68	34 ± 8	473 ± 57
TFP	28 ± 6	274 ± 43*	17 ± 4	257 ± 55*	21 ± 5	337 ± 50
Spermidine						
Control	889 ± 31	832 ± 66	1078 ± 63	1186 ± 104	1005 ± 47	1148 ± 36
TFP	791 ± 37	779 ± 79	1086 ± 64	1056 ± 120	1019 ± 41	1006 ± 102
Spermine						
Control	1021 ± 16	794 ± 21	917 ± 46	793 ± 48	837 ± 40	732 ± 38
TFP	976 ± 19	841 ± 49	990 ± 49	776 ± 29	876 ± 49	726 ± 51

Values represent the mean ± s.e.m. in nmol/g wet weight from 6–7 animals per group. TFP, trifluoperazine dihydrochloride (60 mg/kg BW), Hx, hepatectomy, * $P < 0.05$ *versus* control

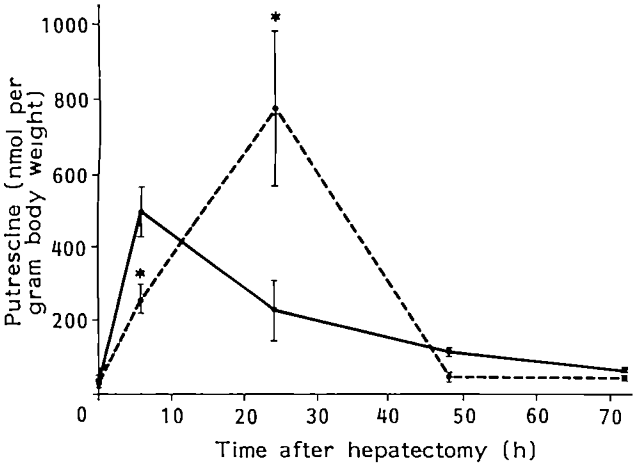

Figure 1 *Effect of trifluoperazine dihydrochloride (TFP) (60 mg/kg BW) on putrescine concentration when TFP was administered at the time of hepatectomy. Values represent the mean ± s.e.m. from 6–8 animals per group* * $P < 0.05$ versus *control*

Experiment 1 Thirteen adult male Sprague-Dawley rats (213 ± 33 g) were divided into two groups, control ($n = 6$) and TFP ($n = 7$). A subcutaneous injection of either saline (1 ml/kg body weight) or TFP (60 mg/kg body weight) was given at time of partial hepatectomy The remaining liver was removed at reoperation 6 h later.

Experiment 2 Thirteen adult male Sprague-Dawley rats (274 ± 13 g) were divided into two groups, control ($n = 6$) and TFP ($n = 7$) A subcutaneous injection of either saline (1 ml/kg body weight) or TFP (60 mg/kg body weight) was administered 2 h before partial hepatectomy. The remaining liver was taken at reoperation 6 h after partial hepatectomy.

Experiment 3. Twelve adult male Sprague-Dawley rats (193 ± 24 g) were divided into two groups, control ($n = 6$) and TFP ($n = 6$) Each group received a subcutaneous injection 2 h after partial hepatectomy of either saline (1 ml/kg body weight) or TFP (60 mg/kg body weight). The remaining liver was taken 6 h after partial hepatectomy.

Experiment 4 Fourteen male Sprague-Dawley rats (246 ± 14 g) were divided into two groups, control ($n = 7$) and TFP ($n = 7$). Each group received a subcutaneous injection of either saline (1 ml/kg body weight) or TFP (60 mg/kg body weight) at the time of partial hepatectomy The remaining liver was excised 24 h later.

Experiment 5 Fourteen male Sprague-Dawley rats (261 ± 12 g) were divided into two groups, control ($n = 8$) and TFP ($n = 6$) Each group received a subcutaneous injection of either saline (1 ml/kg body weight) or TFP (60 mg/kg body weight) at the time of partial hepatectomy The remaining liver was taken 48 h later.

Experiment 6. TFP given at time of partial hepatectomy. Twelve male Sprague-Dawley rats (261 ± 12 g) were divided into two groups, control ($n = 6$) and TFP ($n = 6$). Each group received either saline (1 mg/kg body weight) or TFP (60 mg/kg body weight) subcutaneously at the time of partial hepatectomy. The remaining liver was excised 72 h later

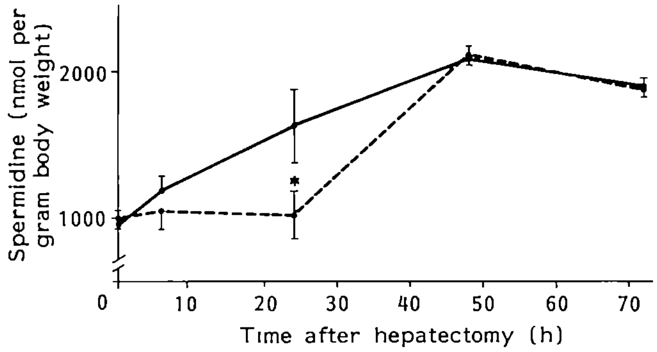

Figure 2 *Effect of trifluoperazine dihydrochloride (TFP) (60 mg/kg BW) on spermidine concentration when TFP was administered at the time of hepatectomy Values represent the mean ± s.e.m. from 6–8 animals per group.* * $P < 0.05$ versus *control*

Results

Experiments 1, 2 and 3 were performed to examine the effect of varying the time of TFP (60 mg/kg BW) administration on polyamine biosynthesis and liver regeneration at 6 h post-hepatectomy.

TFP, when administered 2 h before or at the time of hepatectomy, reduced the elevation of putrescine levels which normally occur 6 h after hepatectomy (*Table 1*). The extent of inhibition when TFP was given 2 h before hepatectomy (53 per cent) and when TFP was given at the time of hepatectomy (48 per cent) was similar. On the other hand, when TFP was injected 2 h after hepatectomy, there was no significant decrease in putrescine when compared with control values (*Table 1*). Spermidine and spermine values were not significantly different 6 h post-hepatectomy, regardless of the time of TFP administration (*Table 1*).

Experiments 1, 4, 5 and 6 examined the effect of TFP (60 mg/kg BW) administered at the time of hepatectomy on polyamine biosynthesis at 6, 24, 48, and 72 h after partial hepatectomy TFP delayed (shifted to the right) elevations of putrescine. Maximal putrescine concentrations in the control group were observed 6 h post-hepatectomy (*Figure 1*), whereas, in the TFP-treated rats, maximal putrescine values were observed at 24 h. Spermidine was significantly inhibited at 24 h (38 per cent), but returned to normal levels at 48 h (*Figure 2*). Spermine was not significantly altered at any point during the experiments.

Liver regeneration was measured by wet weight and as the calculated percentage of pre-hepatectomy weight. Liver regeneration was significantly delayed in the TFP group, with

Table 2 *Effect of trifluoperazine (60 mg/kg BW) on regenerating liver expressed as weight and as percentage of the calculated pre-hepatectomy weight*

	Liver weight			
	6 h	24 h	48 h	72 h
Control (g)	1·65 ± 0·19	3·24 ± 0·25	5·06 ± 0·23	6·26 ± 0·26
TFP (g)	1·89 ± 0·14	3·11 ± 0·18	4·15 ± 0·20*	4·83 ± 0·23*
Control (%)	32·9 ± 3·0	45·5 ± 3·8	70·5 ± 3·2	83·2 ± 4·5
TFP (%)	35·7 ± 2·4	41·7 ± 2·3	54·1 ± 2·6*	65·3 ± 1·1*

TFP, trifluoperazine, * $P<0·05$ *versus* control. Values represent the mean ± s.e.m from 6–8 animals per group

inhibition observed at 48 and 72 h after partial hepatectomy (*Table 2*).

Discussion

The normal process of liver regeneration is characterized by significant elevations in concentrations of polyamines[6,7] and calmodulin[22] 6–8 h after partial hepatectomy Both polyamines and calmodulin are involved in mechanisms of cellular proliferation[1–4,17]. Our results show that the calcium–calmodulin blocker, TFP, given to rats at the time of, or 2 h before partial hepatectomy, significantly decreased putrescine levels at 6 h after partial hepatectomy. When TFP was given 2 h after partial hepatectomy, however, no alterations of putrescine levels were observed.

In addition, TFP given at the time of partial hepatectomy delayed the putrescine elevation normally seen in controls at 6–24 h. This delay may be attributed to TFP-induced inhibition of the calcium–calmodulin complex and subsequent inhibition of polyamine synthesis. Recovery of the calcium–calmodulin complex after a single bolus injection of TFP was reflected in resumption of polyamine biosynthesis. Spermidine in the TFP-treated rats was inhibited at 24 h, reflecting the earlier inhibition of putrescine (a spermidine precursor).

Liver regeneration was measured by wet weight and was also expressed as the percentage of the calculated pre-hepatectomy weight. Inhibition of liver regrowth was observed at both 48 and 72 h in the TFP-treated rats. TFP previously has been shown to inhibit DNA synthesis in regenerating rat liver when it was administered 4 h after partial hepatectomy[25], and it has been shown to block calcium-stimulated DNA synthesis in T51B rat liver cells[19]. The likely mechanism of TFP-induced inhibition of liver regeneration is through inhibition of the calcium–calmodulin complex, which appears to be an early event preceding both polyamine and DNA biosynthesis.

The calmodulin complex is thought to act as a growth modulator. Calmodulin has been shown to stimulate the synthesis of DNA in rat liver cells *in vitro*[19], as well as being found in increased amounts in the SV40-transformed Swiss 3T3 cell line[21]. Polyamines are required for most forms of cellular proliferation; increased amounts of polyamine have been found after partial hepatectomy[6,7], in rat hepatoma[3,26], and in other neoplastic tissues[3]. The importance of our study is that by using TFP, an agent that blocks the calmodulin complex, we have shown that calmodulin is required for both the synthesis of polyamines and subsequent liver regeneration. The event which initiates cellular proliferation remains obscure, but by identifying early events in this process, we hope that the mechanisms can be fully demonstrated.

We have shown the calcium–calmodulin complex to be essential for polyamine biosynthesis and subsequent DNA synthesis. These findings implicate the calcium–calmodulin complex as an important regulator of polyamine metabolism and cellular proliferation.

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Management of symptomatic gallstones in the elderly

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In a study of 544 patients with symptomatic gallstones 158 subjects were aged >70 years. Elderly patients had a significantly higher incidence of emergency presentation, jaundice, cholangitis, ductal stones, biliary drainage procedures, and acute complications requiring urgent or emergency surgery ($P < 0{\cdot}001$)*; they had more than twice the incidence of postoperative complications in comparison with patients aged <70 years. There was an increased perioperative mortality in the elderly (1·3 per cent after cholecystectomy and 2·9 per cent after bile duct exploration,* $P = 0{\cdot}039$)*. Conservative treatment in 11 per cent of elderly patients resulted in no mortality due to gallstones, but 3 of 17 patients had recurrent biliary symptoms. It was estimated that 38 per cent of the bile duct explorations in the elderly might have been avoided by referral for endoscopic sphincterotomy, but surgical treatment of gallstones in the district general hospital is relatively safe and specialist referral should be considered only in the relatively small number of 'high risk' cases.*

Keywords: Gallstones, choledocholithiasis, sphincterotomy, endoscopy

Surgical operations for gallstones are associated with increased perioperative mortality in the elderly[1–7], and mortality rates approaching 30 per cent have been reported after bile duct explorations in elderly patients[1]. The risks attached to such surgery have resulted in an increasing enthusiasm for the use of endoscopic sphincterotomy in the management of symptomatic ductal stones, and it has been suggested that surgery may be avoided in many elderly patients by the use of this technique[8–10]. Unfortunately, few hospitals in the UK presently possess such an endoscopic service[11], and surgery is the only treatment available for most patients with symptomatic gallstones. But are the results of surgery as bad as some of the published reports suggest? Should we refer our elderly patients with gallstones to regional or subregional centres possessing the expertise for endoscopic sphincterotomy and, if so, how many patients would need to travel? We have addressed these questions as part of a prospective study of 544 patients with symptomatic gallstones.

Patients and methods

Between 1978 and 1987, 544 consecutive patients admitted to this unit with symptomatic gallstones (excluding those with gallstone-associated pancreatitis) were entered into the study. Data collected prospectively by one of the authors (T.T.I) included the mode of admission (elective or emergency), the nature of the presenting illness, the clinical, laboratory and operative findings, the methods of surgical treatment, postoperative complications, and the perioperative (30 day) mortality rate

The surgical operations were performed by one consultant surgeon or by one of several junior staff of registrar or senior registrar status. A two-dose regimen of systemic antibiotic prophylaxis was used in all cases, and longer courses of antibiotics were used in cases of established biliary infection. Low-dose subcutaneous heparin was used in the prophylaxis of thrombo-embolism in patients with a previous history of such complications or in very obese subjects, and all patients used compression stockings. Jaundiced patients were given pre-operative intravenous fluid loading, and a peroperative diuresis was maintained with intravenous mannitol

The clinical status of patients managed conservatively without a surgical operation was established from the case records or by enquiries to the general practitioners

For the purpose of the study the patients were divided into two groups according to their age on presentation: a group of 158 patients aged >70 years, and a group of 386 patients aged <70 years Statistical comparisons were made using the χ^2 test, the unpaired Student's t test, and Fisher's exact test.

Results

The group of 158 elderly subjects comprised 64 men and 94 women of average age 78 years (range 70–93), and the group of 386 patients aged <70 years comprised 133 men and 253 women of average age 50 years (range 20–69).

Mode of admission, presenting illness, and treatment (Table 1)
Elderly patients had a significantly higher rate of emergency admission ($\chi^2 = 43{\cdot}33$, $P < 0{\cdot}001$) and a significantly higher incidence of serious complications requiring emergency or urgent surgery, including gangrene or perforation of the gallbladder, jaundice, and cholangitis ($\chi^2 = 27{\cdot}79$, $P < 0{\cdot}001$). Acute cholecystitis occurred in 31 patients presenting as emergencies with classical clinical features, the diagnosis being confirmed by ultrasound examination of the gallbladder and/or the findings at surgery. A majority of patients in both groups had a chronic illness not requiring urgent or emergency admission to hospital: in most cases these patients experienced typical biliary pain and associated intolerance of fat.

We used elevated serum creatinine (>130 μmol/l), low serum

Table 1 *Mode of presentation, presenting illness, and methods of treatment in the two groups of patients*

	Age >70 years (n = 158)		Age <70 years (n = 386)	
Emergency admission	63	(40)	55	(14)
Presenting illness				
Perforation of gallbladder	6	(4)	—	
Gangrene of gallbladder	3	(2)	—	
Empyema	5	(3)	4	(1)
Jaundice	13	(8)	12	(3)
Cholangitis	6	(4)	4	(1)
Acute cholecystitis	19	(12)	12	(3)
Biliary colic	11	(7)	23	(6)
Chronic symptoms	95	(60)	331	(86)
Risk factors				
No. of patients	10	(6)	9	(2)
Serum bilirubin >100 μmol/l	8		5	
Serum albumin <30 g/l	7		7	
Serum creatinine >130 μmol/l	5		3	
Treatment				
Surgical	141	(89)	381	(99)
Conservative	17	(11)	5	(1)

Figures in parentheses are percentages

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Table 2 *Methods of surgical treatment in the two groups of patients*

	Age >70 years		Age <70 years	
No of operations	145		384	
Operation				
Cholecystectomy alone	76		307	
Common bile duct exploration ± cholecystectomy	69*	(48)	77	(20)
Positive common bile duct exploration	61		65	
Common bile duct drainage procedure				
Total	27*	(19)	26	(7)
Transduodenal sphincterotomy	14		18	
Choledochoduodenostomy	12		7	
Hepaticodochojejunostomy	1		1	

Figures in parentheses are percentages; * significantly higher incidence in patients aged >70 years, $P < 0{\cdot}001$

albumin (<30 g/l), and high serum bilirubin (>100 μmol/l) values as indicators of high risk in biliary surgery[4]. Such abnormalities occurred in 4 per cent of patients in this study, and there was a significantly higher incidence of risk factors (6 per cent) in the elderly ($\chi^2 = 4{\cdot}20$, $P < 0{\cdot}05$).

Outcome of conservative treatment

In all, 22 patients admitted as emergencies did not undergo a surgical operation in this unit: 18 were not offered surgery either because of advanced age (13 patients) or because they had serious co-existing medical disorders (5 patients), and 4 patients refused surgery The clinical progress of these patients has been monitored during an average follow-up period of 5·1 years (s.d. ± 3·6 years) of the 17 patients aged >70 years, 6 have died from unrelated causes, 8 are asymptomatic, 2 have occasional biliary pain, and 1 patient has undergone a successful cholecystectomy elsewhere.

Methods of surgical treatment (Table 2)

Operations (529) were performed in 522 patients, and 7 patients (1·3 per cent) required a second operation for residual or recurrent bile duct stones.

Operative cholangiography was performed in 423 operations (80 per cent). Failure to perform cholangiography was attributable to the presence of tiny cystic or extrahepatic bile ducts in 63 cases, technical failure in 31 cases, and severe inflammatory changes in 12 cases. The proportion of operations accompanied by a cholangiogram was virtually identical in both groups of patients (79 per cent of operations in patients aged >70 years, and 81 per cent of operations in patients aged <70 years).

There was a significantly higher incidence of common bile duct explorations and biliary drainage procedures in elderly subjects ($P < 0{\cdot}001$), and a slightly lower incidence of negative duct explorations in the elderly. Elderly subjects also had a slightly higher incidence of inflammatory strictures of the bile duct (1·9 per cent of elderly patients, and 0·8 per cent of patients aged <70 years).

Mortality and morbidity (Table 3)

Operations in patients aged >70 years were associated with increased perioperative mortality ($P = 0{\cdot}039$): there were three deaths in this study, and all occurred in elderly patients. The mortality rate in patients aged >70 years was 1·3 per cent after cholecystectomy alone, and 2·9 per cent after bile duct exploration. The single death after cholecystectomy occurred in a relatively fit 76-year-old man who inhaled gastric contents several hours after surgery. The two deaths after bile duct exploration occurred in elderly women (aged 80 and 81 years) suffering from identical complications of gallstones: both had ductal stones, inflammatory strictures of the common hepatic duct, jaundice, and cholangitis; both died from hepatorenal failure after cholecystectomy and choledocholithotomy with dilatation and T tube splinting of the biliary stricture. In each case death was attributable to postoperative biliary sepsis and, in retrospect, it seems probable that both patients might have been better served by a definitive procedure for the biliary stricture. However, both patients were deeply jaundiced and had significant pre-operative disturbances of their plasm proteins and renal function; they were in a high risk category according to the criteria of Blamey *et al.*[4].

The average duration of stay for elderly patients (13·4 ± 5·5 days) was significantly greater than that of patients aged <70 years (10·4 ± 2·4 days) ($P < 0{\cdot}01$), and the incidence of postoperative complications in the elderly (17 per cent) was more than double that of patients aged <70 years (7 per cent) ($\chi^2 = 10{\cdot}18$, $P < 0{\cdot}01$). Interestingly, the complication rate after exploration of the bile duct was similar to that following cholecystectomy alone in both groups of patients (16 per cent for common bile duct exploration and 17 per cent for cholecystectomy in the elderly; 8 per cent for common bile duct and 7 per cent for cholecystectomy in patients aged <70 years). Respiratory and abdominal wound complications were most frequently encountered after biliary surgery, but the overall incidence of wound infection (1·5 per cent) and burst abdomen (0·4 per cent) was acceptably low. The diagnosis of wound infection was confined to patients discharging pus from the abdominal incision, and both cases of burst abdomen in this study were confirmed at a resuture operation. The respiratory complications in this study included cases of sputum retention with fever and signs of atelectasis, and one patient who required assisted ventilation after inhalation of gastric contents (the single death following cholecystectomy).

The increased morbidity in the elderly is largely attributable to an increased incidence of respiratory and cardiac complications and to residual or recurrent bile duct stones Several patients developed cardiac arrhythmias or signs of congestive cardiac failure following surgery, but there were no cases of postoperative infarction. There was a low incidence of postoperative deep vein thrombosis in this study, but it should be noted that the diagnosis was based on clinical signs rather than on the findings in venography or radio-isotopic studies. One patient aged <70 years had a pulmonary embolism, the diagnosis being confirmed by a pulmonary perfusion scan.

Eligibility for endoscopic sphincterotomy (Table 4)

Although elderly patients had a higher incidence of ductal stones compared with patients aged <70 years, they also had a higher incidence of gangrene or perforation of the gallbladder and of severe attacks of acute cholecystitis resulting in urgent or emergency surgery. These acute cases would not have been

Table 3 *Postoperative morbidity in the two groups of patients*

	Age >70 years		Age <70 years	
No. of operations	145		384	
No. with complications	24	(11)	28	(6)
Complications				
Total	27	(15)	33	(6)
Burst abdomen	1		1	
Wound infection	2	(1)	6	(1)
Wound haematoma	1		1	(1)
Respiratory complications	7	(3)	5	
Urinary retention	3	(1)	3	(1)
Cardiac/renal complications	5	(4)	2	
Hepatic failure	2	(2)	—	
Further laparotomy (sepsis, bleeding, or bile leak)	1	(1)	3	
Calf vein thrombosis	—		4	
Pulmonary embolism	—		1	
Postoperative ileus	—		2	
Confusional state	1		1	
Biliary fistula	—		1	(1)
Residual or recurrent bile duct stone	4	(3)	3	(2)

Figures in parentheses are numbers occurring after bile duct explorations

Table 4 *Estimated incidence of common bile duct explorations which could have been avoided by endoscopic sphincterotomy*

Common bile duct explorations	Age >70 years		Age <70 years	
No of positive explorations	61		65	
Urgent or emergency operation	35		12	
Common bile duct stricture	3		3	
Uncomplicated (suitable for endoscopic sphincterotomy)	23*	(38)	50	(77)

Figures in parentheses are percentages; * significantly lower incidence of explorations in patients >70 years, $P < 0.001$

eligible for treatment by endoscopic sphincterotomy, and it is doubtful if elderly patients with inflammatory strictures of the bile duct would have benefited from endoscopic treatment[12]. We have estimated that only 38 per cent of the bile duct explorations in the elderly might have been avoided by referral for endoscopic treatment, although a significantly higher proportion (77 per cent) of the explorations in patients aged <70 years might have been avoided ($\chi^2 = 19{\cdot}86$, $P < 0{\cdot}001$). However, only 2 of the 19 patients with 'high risk' biochemical parameters (both aged >70 years) would have qualified for referral according to this assessment.

Discussion

Previous studies of cholelithiasis in the elderly have noted a high incidence of complications and an increased perioperative mortality in this age group[1–7]. Elderly subjects in the present study had a significantly higher rate of emergency presentation with severe attacks of acute cholecystitis, gangrene or perforation of the gallbladder, and a significantly higher incidence of ductal stones, jaundice, and cholangitis. The perioperative mortality rate in the elderly was significantly greater than that of patients aged <70 years, but it was lower than some previous reports of the mortality in elderly subjects: McSherry and Glenn[2] reported a 5 per cent mortality rate in operations for gallstones in patients aged >65 years; Houghton *et al.*[6] encountered a 3 per cent mortality rate in this age group; and Addison and Finan[7] reported a 10 per cent mortality rate after urgent or emergency cholecystectomy in patients aged >70 years. Bile duct exploration has been associated with even higher mortality rates in the elderly: 29 per cent in the study of Vellacott and Powell[1] and 21 per cent in the series of Duron *et al.*[5].

The perioperative mortality rate in patients aged >70 years in the present study was 2 per cent overall, 1·3 per cent after cholecystectomy alone, and 2·9 per cent after bile duct exploration. Several factors might account for the lower mortality rate in the present study, including the relatively low incidence of 'high risk' subjects undergoing surgical treatment and the policy of avoiding surgery when possible in unfit subjects. Only 6 per cent of the elderly patients had elevated serum creatinine, high serum bilirubin, or low serum protein levels and were 'high risk' according to the criteria of Blamey *et al.*[4]. A conservative treatment policy was adopted in 17 elderly subjects (11 per cent) and no patient died from complications related to gallstones, although 3 of the 17 patients had further symptoms.

The postoperative morbidity in this study was substantially lower than in some recent accounts of the complications of surgery for gallstones[1,13,14]. Complication rates of 44–46 per cent have been reported after bile duct exploration[13,14], much of the morbidity being related to cardiorespiratory and septic complications. The lower incidence of septic complications in this study may be attributable to the routine policy of antibiotic prophylaxis, and it is possible that prophylactic measures were also successful in avoiding thrombo-embolic complications. Surprisingly, the morbidity after bile duct exploration was not significantly different from that resulting from simple cholecystectomy However, the morbidity was age-related, and elderly subjects experienced a significantly higher incidence of complications after all types of biliary surgery.

We believe that the results of the present study are reasonably representative of the standards that may be expected in any surgical unit in a district general hospital. This unit is one of four general surgical units serving a population of approximately 250 000, and it professes no special expertise in biliary tract surgery; nor is there any reason to believe that the unit experiences an unusual referral pattern. It is against this background that the question of referral of elderly patients with ductal stones to specialist units for endoscopic sphincterotomy must be considered. It has been suggested that this is the treatment of choice for ductal stones in the elderly although there is some disagreement over whether it is necessary to remove the gallbladder after successful endoscopic treatment[8–10,15]. Hospital mortality rates of 1–11 per cent have been reported after endoscopic sphincterotomy[8,16], but not all of the mortality is a direct consequence of the endoscopic treatment, and the high mortality rates are a reflection of the high ratio of medically unfit or 'high risk' subjects in most series[16] In the present study 38 per cent of bile duct explorations in the elderly might have been avoided by referral for endoscopic sphincterotomy. However, it is doubtful if regional or subregional specialist units could cope with the workload if this policy of referral was adopted by all surgical units in district general hospitals. Fortunately, the situation is not as serious as earlier mortality statistics relating to biliary tract surgery suggested. There is very little risk involved in operations for gallstones in the majority of cases, and referral to specialist centres need be considered only for the relatively small number of 'high risk' patients.

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Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial

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A total of 52 jaundiced elderly patients who had malignant obstruction of the distal common bile duct and who required palliative biliary decompression were randomized to receive either an endoscopically placed biliary endoprosthesis (10 French gauge) or conventional surgical bypass. Patients within the two treatment groups were well matched and 51 were followed until their death. Patients treated with endoprosthesis had a significantly shorter initial hospital stay than those treated surgically. In the long term, overall survival in the two groups was similar and jaundice was relieved in over 90 per cent of patients. Despite more re-admissions to hospital for those patients treated endoscopically, the total time spent in hospital still remained significantly shorter in this treatment group compared with those subjected to surgery. The endoscopically placed biliary endoprosthesis is a valuable alternative to conventional surgical bypass in the palliation of extrahepatic biliary obstruction.

Keywords: Carcinoma of pancreas, common bile duct, endoscopy

The incidence of carcinoma of the pancreas is increasing in the UK and is the commonest cause of malignant obstruction of the extra-hepatic biliary tree. Carcinoma of the head of the pancreas has a very poor prognosis and palliative treatment is all that can be offered for most patients presenting with malignant obstruction of the extrahepatic biliary tree[1,2]. Pancreatectomy has a high operative mortality and some patients palliated with bypass surgery live longer than those patients who have had a resection[3,4].

Although surgical decompression of the biliary tree by biliary enteric anastomosis is still the main palliative procedure performed, non-surgical methods of biliary decompression are being used increasingly. In the latter procedure, polyethylene or TEFLON® (Du Pont, UK) endoprostheses (stents) may be introduced into the biliary tree by the transhepatic or transduodenal routes[5–8]. The endoprostheses are positioned within the bile duct by railroading them over a guide wire and dilating tube assembly which has been negotiated through the obstruction.

At present the optimal size and shape of an endoprosthesis appears to be a straight, 10 or 11·5 French gauge polyethylene tube, tapered at one end and with retaining barbs at either end.

Clinical results from uncontrolled studies, which have included a heterogeneous group of patients, have suggested that the procedural morbidity and mortality for treatment with the endoprosthesis is as good as surgery in the palliation of malignant biliary obstruction[7–9].

To date, only one prospective controlled trial has been undertaken which has compared conventional surgical bypass with transhepatically placed endoprosthesis; it has shown that the non-operative technique is as good as surgery for palliating malignant biliary obstruction[10].

The aim of the endoprosthesis study was to determine whether endoscopically inserted endoprosthesis was a real practical alternative to surgical bypass in patients in whom only a palliative procedure was deemed possible. The study prospectively compared biliary decompression with these two techniques in a randomized group of patients who had malignant obstruction of the common bile duct

Patients and methods

Between 1984 and 1986, patients with a clinical diagnosis of primary malignant obstruction of the extrahepatic biliary tree, and in whom curative surgery was not contemplated by the referring consultant, were eligible for entry into the study. Patients were investigated further in one of three Wessex hospitals: the Royal Hampshire County Hospital, Winchester, UK, Southampton General Hospital, Southampton, UK; and Queen Alexandra Hospital, Portsmouth, UK. Pre-entry assessment of patients included clinical examination, blood biochemistry and haematology. The biliary tree and pancreatic duct were visualized using ultrasound scan, CT scan if considered necessary and endoscopic retrograde cholangiopancreatography (ERCP).

At ERCP every effort was made to visualize both pancreatic and biliary duct systems, evidence of obliterative involvement of both ducts being taken as diagnostic of carcinoma of the pancreas, otherwise, the demonstration of a shouldered common bile duct stricture[11] with supporting evidence of malignancy from the ultrasound scan and clinical details were considered diagnostic Finally, fine needle aspiration cytology was undertaken whenever possible to confirm the diagnosis, but this was not necessarily performed pre-operatively, particularly when a confident diagnosis could be made on clinical criteria and radiological imaging. Angiography was not performed.

All patients received ERCP as their final investigation before randomization but they were not randomized until at least a cholangiogram had been obtained. In the absence of duodenal encroachment by the malignancy, the criteria for entry into the study required the demonstration of a malignant obstruction of the common bile duct which was considered technically suitable for treatment either by surgical bypass with cholecystostomy or choledochoduodenostomy, or with an endoprosthesis which could be positioned endoscopically to lie across the obstruction.

Patients were excluded from randomization if the ERCP failed to visualize the biliary tree, if the patient was unfit for a general anaesthetic or if the tumour arose from the papilla itself; these tumours were often palliated by sphincterotomy alone Patients with duodenal stenosis were treated surgically and those with overt disseminated malignancy were treated with endoscopic endoprosthesis

Pre-operatively, patients in both groups were treated with intravenous fluid replacement as necessary and any clotting abnormalities were corrected with vitamin K. Patients randomized to receive an endoprosthesis were given a second-generation cephalosporin antibiotic, intravenously, at the time of the placement of the endoprosthesis and this was continued for 3 days. Patients treated surgically received a single dose of 1·5 g cefuroxime intravenously together with 20 ml 20 per cent mannitol at induction

All surgery was performed at the referring hospital and no restrictions were imposed regarding the type of bypass procedure performed

At endoscopy a 10 French gauge polyethylene endoprosthesis (Wilson Cook, Europe) was inserted using a coaxial insertion system by one of three endoscopists (H A S , M A , D C.-J.) at the respective referral centres using a 3·7 mm working channel duodenoscope (Pentax FD34H or Olympus JF 3.7T). Practical details of this procedure have

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been described before [7–9,12].

The protocol allowed for cross-over of patients into the other group after failure of the primary randomized treatment. At least two attempts to insert the endoprosthesis were made within a week of each other. Those patients who returned with jaundice due to blockage of their first endoprosthesis received replacements.

Results

The criteria for entry into this study resulted in the selection of a group of patients who had malignant obstruction of the distal common bile duct and who required only palliative decompression of the biliary tree.

A total of 90 consecutive patients were referred for further investigation of presumed malignant biliary obstruction, of whom 52 (58 per cent) were randomized.

Table 1 illustrates the details of 38 patients (42 per cent) who were excluded from randomization. Included within this group were 18 patients who were not randomized and who received specific treatment at the instruction of the referring consultant. This was an unavoidable event when the study was accruing patients from all of those referred for further cholangiographic assessment of their obstructive jaundice. However, of these 18 patients only 10 would have been suitable for entry into the study.

Of the 52 patients, 25 were randomized to receive surgical bypass and 27 to receive endoprosthesis. Of those randomized, two patients in the surgical group were withdrawn, one died pre-operatively and in one case a Whipple's operation was attempted at the laparotomy. The operative procedures performed in the surgical group were as follows: cholecystojejunostomy and gastrojejunostomy (four patients); cholecystojejunostomy with jejunojejunostomy and gastrojejunostomy (nine patients); choledochojejunostomy and gastrojejunostomy (eight patients); and choledochojejunostomy alone (two patients). There were two technical failures in the surgical group when tumour prevented the formation of a satisfactory anastomosis despite acceptable pre-operative cholangiograms. These patients later were successfully treated by endoprosthesis. The overall technical success for surgical bypass was 92 per cent.

In those patients randomized to receive endoprosthesis, one was withdrawn after two successive biopsies were considered benign despite ultrasound and CT scans and a cholangiogram suggesting carcinoma of the head of the pancreas. Later he had a laparotomy where an infiltrating carcinoma was discovered.

Technical success in the endoscopy group was achieved in 82 per cent with four failures in patients who subsequently underwent successful surgical bypass. An endoprosthesis insertion failed in a single patient in whom previous surgery had also failed

Table 2 gives the details of the randomized patients in the study All patients in the surgical group were found to have a mass in the head of the pancreas.

Table 3 shows the short-term results. A 30-day period after the surgical or endoscopic procedure has been chosen to look at the short-term (periprocedural) deaths; these patients died in hospital during their first admission. Although not statistically significant, there was a trend towards improved 30-day survival in the endoscopic group. In those patients who survived more than 30 days, the periprocedural hospital stay was significantly shorter in those randomized to endoprosthesis. Procedural complications (events) in five patients of the endoscopic group included cholangitis (four), chest infection (one), pain in the right upper quadrant (one) and a single episode of melaena.

Table 1 *Details of those patients with malignant biliary obstruction who were excluded from randomization*

Exclusion criteria	Number ($n = 38$)	Proportion of group (%)
Non-randomized treatment* (treatment decided before ERCP)	18	47
Duodenal stenosis	4	10
Porta block	8	21
Disseminated malignancy	4	10
Carcinoma of papilla	2	5
Failed ERCP	2	5

*Non-randomized group suitable for trial, 10; porta block, 3, failed ERCP, 1; ampullary carcinoma, 1; unfit for surgery, 3

Table 2 *Details of patients in the two study groups*

	Stent ($n = 23$)	Surgery ($n = 25$)
Male	10	17
Female	13	8
Age (mean years)	72·8 (61–89)	73·2† (56–87)
Bilirubin: patients >300 mol/l	10	14
Mean of patients' bilirubin <300 mol/l (normal, <17 mol/l)	195 (70–272)	222† (56–298)
Mean albumin (g/l) (normal, 32–40 g/l)	35·3 (26–40)	33·8† (27–40)
Abnormal pancreatograms	18 (78%)	18 (72%)
Biopsy confirmation of malignancy	11 (48%)	17 (68%)

†χ^2 test: not significantly different stent *versus* surgery. Except where stated, values in parentheses are ranges

Table 3 *Short-term results*

	Stent ($n = 23$)	Surgery ($n = 25$)
Initial hospital stay for patients alive >30 days (median days and range)	5·0 (2–16)	13·0 (8–49)*
Patients alive >30 days	21	20
30-day mortality	2 (9%)	5 (20%)†
Procedural complications (events)	7	14†

*Mann–Whitney *U* test: $P < 0·002$, stent *versus* surgery; †χ^2 test: not significant, stent *versus* surgery The median and range of hospital stay are given

In the surgical group, fourteen complicating events occurred in ten patients; these were two gastrointestinal bleeds, two wound and four chest infections, and single instances of a subphrenic abscess, stroke, postoperative gastric stasis, diarrhoea, intestinal obstruction and an anastomotic leak of infected bile. The last two patients required re-operation.

In the long term, both techniques were effective at relieving jaundice (biochemical bilirubin level up to three times normal; *Table 4*).

The overall survival of patients did not differ significantly between the two groups (*Figure 1*); only one patient in the endoscopic group remains alive.

Before their death, two patients in the endoscopic group (9 per cent) and one patient in the surgical group (4 per cent) developed duodenal stenosis.

Re-admission to hospital was needed on ten occasions for endoprosthesis replacement caused by blockage and cholangitis (*Table 4*). In the surgical group there were three re-admissions, two soon after discharge from hospital for a suspected leaking anastomosis and subphrenic abscess and one for drainage of malignant ascites.

Despite more re-admissions the total hospital stay (days per patient until death) for those patients treated endoscopically was significantly less than those in the surgical group· 8 days and 13 days respectively.

Discussion

This study is the first to report a prospective randomized comparison of endoscopic biliary endoprosthesis with conven-

Table 4 *Long-term results*

	Stent ($n = 23$)	Surgery ($n = 25$)
Overall survival (days)*	152 (39–411)	124 5 (52–354)‡
Relief of jaundice	21 (91%)	23 (92%)
Patients alive (n)	1	0
Survival time (days)	454	—
Long-term results		
One re-admission (n)	7 (30%)	3 (12%)
Hospital stay (days)*	109 (33–240)	(11, 18, 150)
Complications	Cholangitis	Anastomosis leak, vomiting, subphrenic abscess
Two re-admissions	3 (13%)	
Hospital stay (days)	(125, 152, 187)	Nil
Complications	Cholangitis	
Total hospital stay (days per patient until death)*	8 (2–30)	13 (8–49)†

*Median and range values given. Mann–Whitney *U* test (stent *versus* surgery). †$P<0{\cdot}01$, ‡not significant

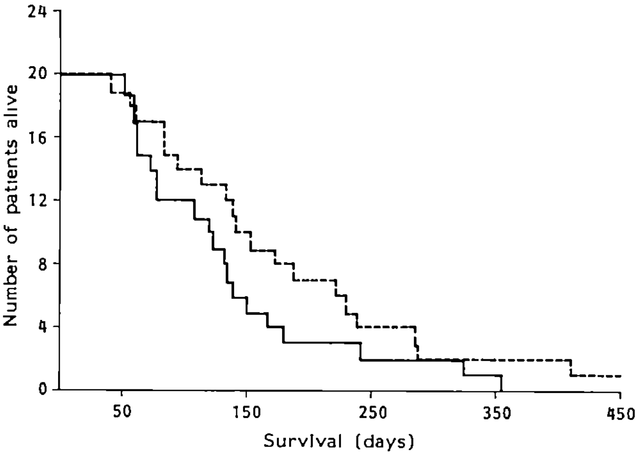

Figure 1 *Life table showing the survival of patients randomized to either surgical bypass (——) or endoprosthesis (- - -)*

tional surgical bypass in the palliation of malignant obstruction of the common bile duct. The design of the study has led to the selection of a group of patients who have obstruction of the distal end of the extrahepatic biliary tree and which could be treated palliatively by either drainage method The two groups were comparable in this respect.

The number of patients excluded from randomization in this consecutive series reflected the variety of pathology that was discovered at ERCP and the influence of a pre-existing stenting service on the management of some of the patients who would have been suitable for randomization.

In the study by Bornman *et al.* (1986), transhepatically placed endoprosthesis was compared with conventional surgical drainage in a group of patients with incurable pancreatic carcinoma but whose mean age was lower than those patients recruited to the present study (mean age 61 7 years compared with 73 years). Their results are similar to those of the present study but in addition showed that even in skilled hands there were serious complications with the transhepatic technique which are not seen with the endoscopic method for endoprosthesis insertion[10,13]. Such complications would be even less well tolerated by older patients.

The present study has shown that a large-bore (10 French gauge) endoprosthesis is as good as surgery in relieving malignant obstructive jaundice but does not affect the overall survival. Furthermore, the time spent in hospital by patients treated with endoprosthesis is significantly shorter than for those patients who have surgery. The exchange of a blocked endoprosthesis will become a less complicated procedure if blockage can be anticipated before jaundice and cholangitis recur.

Although there was a trend towards a lower 30-day mortality for patients treated with endoprosthesis, statistical significance was not reached with the small numbers in the present study. Our experience and that of others[10,14] indicates that the endoscopic method is safer than the wholly percutaneous transhepatic method as there are fewer and less serious procedural complications and failure does not mean obligatory surgery or a permanent external biliary fistula.

The present study confirms the impressions that have been gained from the results of uncontrolled studies that, when technically successful, endoscopically inserted endoprosthesis provides palliation as good as surgery, with the added advantage that for most patients the initial procedure will require a shorter stay in hospital[15]. The late development of duodenal stenosis does not appear to be a major problem.

This trial has shown that in elderly patients presenting with obstructive jaundice due to malignant involvement of the distal extrahepatic biliary tree, and in whom palliation is all that is required, endoscopic insertion of an endoprosthesis to drain the biliary tree is an appropriate procedure. If this fails, then the choice still remains of either surgical decompression or endoprosthesis insertion using a combined percutaneous and endoscopic technique (rendez-vous method)[16].

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Current practice in biliary surgery

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A questionnaire enquiring about current practices in biliary surgery was sent to over 25 per cent of consultant general surgeons in the UK; 90 per cent replied. Only 56 per cent use antibiotic prophylaxis for elective cholecystectomy, and 84 per cent for emergency cholecystectomy. Duration of use, choice of agent and absence of prophylaxis for high-risk cases were inappropriate in up to 20 per cent of cases. Of the respondents 84 per cent routinely perform operative cholangiography and use T tubes, and 75 per cent routinely place a peritoneal drain after cholecystectomy. Despite controversies in the literature, most UK surgeons still follow traditional practices in biliary surgery.

Keywords: Gallbladder, cholecystectomy, bile duct obstruction, extrahepatic

Operations for gallstones and malignant bile duct obstruction constitute a significant part of upper abdominal surgery. Notwithstanding Lawson Tait's assertion in 1885 that 'amongst all the many advances which modern abdominal surgery has seen, I claim that there is none so certain, nor so free from risk, nor so brilliantly successful as the surgical treatment of gallstones'[1], these procedures are still attended by a significant morbidity Wound infection, retained stones and bile duct injury can complicate even 'simple' cholecystectomy, and much has been written in the recent literature about the merits and demerits of antibiotic prophylaxis, operative cholangiography, and drainage to minimize the hazards of biliary surgery. We sought to establish current practice in biliary surgery to assess the influence of these studies on day-to-day surgical techniques.

Methods

A questionnaire was sent to all consultant general surgeons in the four Thames regions, with a reply paid envelope, in March 1987. A further copy of the questionnaire was sent to those who had not replied after 8 weeks The questionnaire sought information about antibiotic usage, operative details and surgery in patients with obstructive jaundice. Section one asked whether or not antibiotics were routinely used during elective cholecystectomy, emergency cholecystectomy, bile duct exploration and in operations for the relief of obstructive jaundice. Details of agents used and duration were requested Section two (operative details) asked whether operative cholangiography, postoperative drainage, T tube insertion after choledochotomy and choledochoscopy were performed routinely, sometimes or not at all. T tube users were asked whether or not antibiotic cover was used for T tube cholangiography Section three enquired about perioperative protection of renal function in patients undergoing surgery for the relief of obstructive jaundice. Surgeons were asked whether or not they use mannitol, pre-operative intravenous fluids and other methods. Details were recorded. The questionnaire was restricted to one side of A4 paper to increase compliance: further important information could have been sought, but it was considered that a short simple form would maximize response.

Results

Two hundred and nine surgeons (80·7 per cent) responded to the first mailing of the questionnaire, and a further 25 to the second approach (90·3 per cent). Twenty-five surgeons did not respond. One respondent declined to answer the questions.

Antibiotic usage

Fifty-six per cent of surgeons use antibiotic prophylaxis for elective cholecystectomy. Three-quarters of these use a cephalosporin, 15 per cent a penicillin, and 10 per cent other agents. Duration of antibiotic usage is shown in *Figure 1*.

Prophylactic antibiotic usage increases to 73 per cent for common bile duct exploration and to 87 per cent for operations on the jaundiced patient. Five per cent of surgeons said they never perform emergency cholecystectomy; only 84 per cent of those who do so use antibiotic prophylaxis. Of the antibiotic users 26 per cent add metronidazole when exploring the bile duct, 28 per cent in jaundiced patients and 26 per cent for emergency cholecystectomy.

Cephalosporins account for >70 per cent of the antibiotics used in all the operative procedures investigated by the questionnaire. The second generation drug cefuroxime is used most commonly (45 per cent of all cephalosporin prescriptions), followed by the first generation drugs cephradine and cephazolin (25 per cent). Unspecified cephalosporins comprise 19 per cent and cefotaxime, a third generation cephalosporin, makes up the remaining 11 per cent. This distribution of cephalosporin usage does not vary significantly between elective and emergency surgery, and many surgeons use the same agent throughout, although the duration of use is longer in the emergency and jaundiced cases (*Figure 1*).

Ampicillin, amoxycillin, and amoxycillin/clavulanic acid are the most commonly used penicillins, each comprising approximately 4 per cent, and only eight surgeons (3·4 per cent) use the ureido penicillins, mezlocillin and piperacillin. The 'other' antibiotics used are gentamicin, metronidazole alone, and combinations of antibiotics described above.

Operative details

Operative cholangiography is performed during elective cholecystectomy routinely by 84 per cent of surgeons, sometimes by 12 per cent and never by 4 per cent. Drains are inserted into the gallbladder fossa after elective cholecystectomy by 75 per cent of respondents, sometimes by 15 per cent and never by 10 per cent. Choledochoscopy is always performed by 33 per cent after bile duct exploration, sometimes by 30 per cent and never by 37 per cent. Eighty-four per cent of surgeons routinely use a T tube after bile duct exploration, 12 per cent sometimes place a T tube, and 4 per cent always close the duct without. Of the surgeons who place a T tube, 13 per cent give antibiotic cover for postoperative cholangiography, 3 per cent sometimes do, and 84 per cent do not.

Protection of renal function in obstructive jaundice

Mannitol is used by 84 per cent of consultant surgeons to protect perioperative renal function in the jaundiced patient. Mannitol is given by 42 per cent pre-operatively (10–100 g, median 25 g), by 63 per cent during surgery (10–200 g, median 35 g), and by 10 per cent after operation (10–200 g, median 45 g). Pre-operative intravenous fluids are given by 71 per cent of surgeons, 12 per cent give pre-operative fluids without a mannitol diuresis and 5 per cent use mannitol without a pre-operative fluid load.

Other methods are used by 14 per cent of consultants. Six per cent of surgeons use bile salts and 3 per cent oral lactulose.

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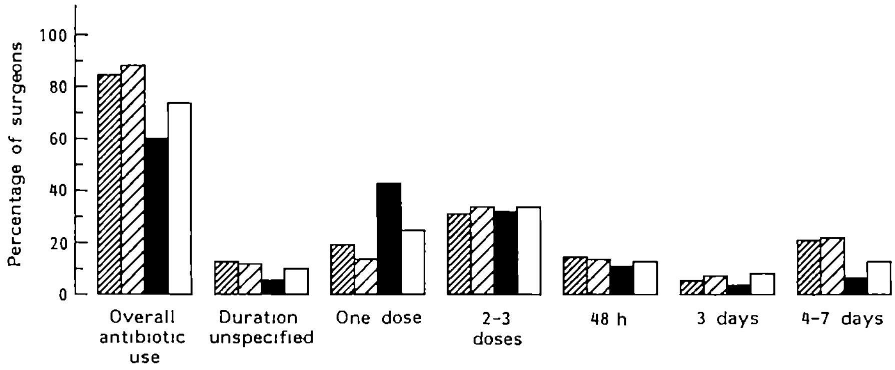

Figure 1 *Duration of antibiotic use for biliary operations* ■, *Emergency cholecystectomy,* ▨, *obstructive jaundice,* ■, *elective cholecystectomy;* □, *bile duct exploration*

Perioperative frusemide is given by 3 per cent and 1 per cent give perioperative dopamine. Oral antibiotics to protect renal function are given by 2 per cent and 1 per cent perform preoperative percutaneous biliary drainage for the same reason

Discussion

Documentation of current surgical practice is an important part of surgical audit. It enables surgeons to compare their methods with those of their peers and also demonstrates the influences of experimental and clinical research. We have circulated this questionnaire to more than 25 per cent of consultant general surgeons in the UK, and the 90 per cent response rate contrasts with only 33 per cent in a recent survey of biliary surgery in the USA[2].

Antibiotic usage

Biliary surgery is attended by a significant incidence of septic complications, particularly wound infection[3]. Bile is colonized by bacteria in 20–40 per cent of patients undergoing elective cholecystectomy[4,5], and in up to 90 per cent with common bile duct stones[6,7] Wound infection has been correlated with the presence of bacteria in the bile[4,5,8], and the same organisms have been cultured from the bile and subsequent parietal infection in a number of studies[3,8]. This is not invariably the case, particularly in patients who have received antibiotic prophylaxis, and staphylococcal wound infection is as prevalent after biliary surgery as after other abdominal operations[9,10].

Wound infection rates of 10–15 per cent are common after elective biliary surgery without antibiotic prophylaxis[3], and can be reduced to <5 per cent with appropriate agents[11–13]. The organisms most commonly isolated from the biliary tract are the coliform bacteria, *Streptococcus faecalis* and the anaerobes *Bacteroides fragilis* and *Clostridium* species. Gram-negative bacilli are most often associated with wound sepsis and, although most are sensitive to cephalosporins, a significant number are now resistant to ampicillin. Antibiotic secretion into bile is less important than adequate serum concentrations in preventing wound infection[14] and the choice of agent appears less important than appropriate timing of administration to ensure adequate tissue levels at operation[15]. Although *S. faecalis* and related organisms are not sensitive to cephalosporins, they do not appear to be important in elective biliary surgery[16,17]. This is not the case in elderly patients, those undergoing re-exploration of the biliary tract after previous surgery, and those recently treated with cephalosporins[18]. The incidence of enterococcal sepsis in these patients is high, and an ureido penicillin such as piperacillin is more appropriate prophylaxis than a cephalosporin.

Anaerobic bacteria have been found in only 6–8 per cent of bile samples unless previous surgery has been performed on the biliary tree[3,19]. Most biliary anaerobes are penicillin sensitive, and metronidazole confers no benefit in the prevention of wound infection after elective cholecystectomy[20].

Although it may seem ideal to identify those patients with bacteria in the bile for antibiotic prophylaxis, selective prophylaxis has been disappointing in practice, with wound infection rates >10 per cent[2], and it cannot be recommended[21]. Some surgeons still believe that good surgical technique cannot be enhanced by antibiotic prophylaxis[22], but a single dose of antibiotic will cover endogenous and exogenous contamination and can reduce the wound infection rate below the 5·3 per cent reported for 'clean' operations[9].

The precise choice of agent appears relatively unimportant, and a single dose is as effective as repeated doses for elective operations[13]. Inexpensive first generation cephalosporins are as effective as the more expensive third generation drugs[23]. Anti-staphylococcal cover is important[24], and the first generation cephalosporins are more active than later cephalosporins. In the jaundiced or high-risk groups, broad spectrum cover including enterococci and anaerobes is necessary. Antibiotic administration intravenously on induction of anaesthesia ensures adequate serum levels during surgery.

Operative details

Cholangiography. There has been a recent, although not universal, trend away from routine to selective operative cholangiography[25–27] in the literature, yet more than 80 per cent of surgeons still routinely perform this investigation during elective cholecystectomy. The main reason cited for operative cholangiography is to reduce the number of negative duct explorations while increasing the proportion of positive explorations. An equally important reason is to help delineate the anatomy of the bile ducts, as more than 70 per cent of bile duct strictures follow a cholecystectomy at which a cholangiogram was not performed[28]. A bile duct stricture is a potential disaster for the patient, and many result from operations considered to be 'uneventful'[29]. Bile duct injury in the absence of a cholangiogram may have medicolegal consequences.

Operative cholangiography is time consuming, expensive and can result in negative duct explorations. Although operative cholangiography is claimed to be safe[30], complications have been reported[31] and cystic duct cannulation may cause bile duct injuries especially in patients with narrow ducts[32]. A selective approach to cholangiography is advocated by those who perform the investigation only in the presence of specified criteria[33–36]. In a series of 346 consecutive cholecystectomies, all of whom had operative cholangiography, 3·5 per cent of cholangiograms showed stones in the common bile duct when none of the above criteria had been met, but a further 1·5 per cent of patients underwent negative duct exploration initiated by the cholangiogram (J.A. Pain, unpublished data) Some increase in the incidence of retained stones after selective cholangiography may be acceptable as many small stones pass spontaneously, and the increasing availability of endoscopic papillotomy and percutaneous extraction make retained stones less of a problem.

Drainage after cholecystectomy. There have been numerous studies investigating whether drainage should or should not be used after elective cholecystectomy, and many have produced conflicting results. Even a recent review has not been able to provide a definite answer[37]. The claimed advantages of drainage are that bile and blood can be drained, and it provides the surgeon with a warning when a clinically significant leakage occurs. The opponents state that drains are often ineffective in these roles[38] and, moreover, it has been shown that postoperative subhepatic fluid collections are more common in patients who have suction drains[39]. As well as the cost and the nursing care required, drains may be associated with increased postoperative pain, wound infections, and respiratory complications[37]. Nevertheless if drains are used it is recommended that they be suction type, be brought out through the skin via a separate incision to the wound and normally be removed within 48 h[37,40–42].

Choledochoscopy after duct exploration. Approximately equal numbers of surgeons always, sometimes or never perform choledochoscopy after bile duct exploration. To a certain extent these figures probably reflect the availability of choledochoscopy rather than the surgeons' preferences, as it is has been clearly demonstrated that the use of either rigid[43] or flexible choledochoscopy[44] can help reduce the incidence of retained stones after exploration. After bile duct exploration the incidence of retained stones is about 10 per cent, but with choledochoscopy this can be reduced to 2–4 per cent[45]. In a recent series of 320 patients undergoing bile duct exploration, operative choledochoscopy revealed further calculi in 7 per cent of patients and the procedure was associated with no complications[46].

T *tube drainage after duct exploration.* Although the majority of surgeons insert a T tube after duct exploration, only 12 per cent sometimes do so and 4 per cent never do. T tubes decompress the bile ducts after exploration, as internal bile drainage may be compromised by oedema or even a retained stone. T tube cholangiography allows later visualization of the biliary tree, and the T tube or its tract can be used as a route to remove retained stones[47]. Duct exploration with primary closure has been advocated by some surgeons[48–50]. Patients with T tubes have prolonged hospital stay, and problems associated with the tube include electrolyte and bile salt depletion, an increased incidence of wound sepsis, pancreatitis, and bacteraemia or bile leakage following its removal[50–53]. To prevent this last problem, the combined diameters of the small limbs of the T tube should be no more than the diameter of the long limb and the T tube should not be removed for at least 10 days after operation[54]. The suitability of chromic catgut as a suture for closure of the choledochotomy has been questioned as it loses 66 per cent of its tensile strength within 10–15 days[54], and a synthetic absorbable suture may be more appropriate. Other problems can be reduced by monitoring plasma electrolytes and giving antibiotic cover at both T tube cholangiography and T tube removal.

Protection of renal function in obstructive jaundice

Renal dysfunction is common after biliary surgery in the jaundiced patient and, in order to help protect against this, most surgeons give intravenous mannitol. In addition more than 70 per cent also rehydrate the patient with intravenous fluids before surgery. We believe rehydration is especially important[55] and should be commenced at least 12 h before surgery; reliance on mannitol alone is inappropriate[56]. Certain oral bile salts and lactulose have been shown in small studies[57–59] to protect renal function and these are at present being further evaluated. A few surgeons use either dopamine or frusemide and, although there may be some theoretical reasons to support their use, they have not been investigated in obstructive jaundice. Oral antibiotics by releasing intestinal endotoxin may in fact be harmful. Randomized studies have shown that pre-operative percutaneous drainage confers no overall benefit to the jaundiced patient[60], but pre-operative internal drainage may be beneficial[61,62].

Despite controversies in the medical literature most surgeons conform to traditional practices in biliary surgery. This is not surprising in areas in which controversy is unresolved, such as drainage after cholecystectomy or routine operative cholangiography. However the evidence for antibiotic prophylaxis is now very considerable but only half the surgeons routinely use antibiotics for elective cholecystectomy.

Historically, changes in surgical practice have often been based on personal experience. With current emphasis on audit, increasing medicolegal awareness, and the comparison of personal results with published data, surgeons may in future be influenced more by their peers' experience than their own. Surgical methods often change imperceptibly, and we hope that this review of biliary techniques now will facilitate documentation of future developments.

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Use of advisers in the diagnosis and management of abdominal pain in accident and emergency departments

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The performance of senior house officers (SHOs) and their advisers in accident and emergency departments was compared in the diagnosis of abdominal pain in 711 patients. Accuracy of diagnosis was 63 per cent for advisers and 54 per cent for SHOs. Overall, the adviser improves the diagnosis of the SHO in only 6 per cent of cases. The SHOs refer accurately in 94 per cent of cases, and the advisers improve the SHO referrals in only 1 per cent of patients. It is argued that the time-consuming process of calling a surgeon away from a ward or theatre to advise in the receiving room is of little value, and avoidance of this step would enable patients to be admitted more rapidly.

Keywords: Abdominal pain, accident and emergency department, diagnosis

The first doctor examining a patient complaining of acute abdominal pain makes a correct diagnosis in only 40–50 per cent of cases[1–4]. It is not surprising that De Dombal (1979)[5] concluded that the performance of these junior doctors, usually senior house officers (SHOs) in the accident and emergency department, left little room for complacency. Diagnostic accuracy improves after investigations and repeated examinations; the pre-operative accuracy of some surgical registrars is as high as 85 per cent[3]. Nevertheless, there is a limit to the diagnostic accuracy that can be achieved on first presentation, though the impressive accuracy of computers indicates that the upper limit is much higher than the level usually achieved. In most UK hospitals, accident and emergency SHOs are required to seek a further opinion from a colleague (referred to here as an adviser) before the patient can be admitted. It is this doctor who is directly responsible for the admission and future management of the patient, not the accident and emergency SHO. The main purpose of this study is to assess the value of an adviser in the diagnosis and management of abdominal pain. The study assesses the diagnostic accuracy of both the junior doctors in the accident and emergency department and of their advisers. We also examined the accuracy of the referrals made by both groups of doctors as this may be a more important indicator of their effectiveness than strict diagnostic accuracy.

Patients and methods

Procedure

The study was carried out in the accident and emergency department of Whipps Cross Hospital between January 1986 and July 1987. Three groups of SHOs were studied, each for 4 months. Within these periods, all patients who complained of abdominal pain on entering the accident and emergency department and who were subsequently admitted were studied (711 patients) The following information was recorded: date and time of registration, age of patient, diagnosis by SHO in the accident and emergency department, further diagnosis in the accident and emergency department by the adviser, and the final discharge diagnosis. The grades and specialities of all the doctors concerned were also recorded.

Assessment of accuracy of diagnosis

The initial diagnosis of the SHO was compared with the final diagnosis, and the accuracy of the initial diagnosis was graded according to a system developed by De Dombal*. In fact De Dombal's table had to be considerably extended to accommodate the range of diagnoses recorded. In the final system, diagnoses were graded from correct diagnosis to very serious error on a scale of 1–6. In the results that follow, correct diagnoses (grade 1) and near misses (grade 2) are both classed as accurate diagnoses, in the sense that no adverse clinical consequences follow from the diagnosis. Grades 3–6 are all classed simply as errors. We have followed De Dombal in scoring cases where no diagnosis was made, as near misses (grade 2) if the final diagnosis is non-specific abdominal pain, and as errors if pathology is found.

Subsequent comparisons of the adviser's diagnosis with the final diagnosis were coded similarly It should be stressed that the diagnoses are rated on the basis of the consequences that would have occurred if they had been acted upon. The rating is a measure of accuracy, not a description of what actually happened.

Accuracy of referral

We also looked at the SHO's diagnosis in terms of the speciality it indicated. In this way we assessed the correctness of the referral that the SHO would have made if the decision had been his or hers to make In the few cases where no diagnosis was recorded, or non-specific abdominal pain was recorded, the referral was judged on the speciality of the doctor called by the SHO or on a second diagnosis, if there was one. Thus 'non-specific abdominal pain/?appendix' would be considered as a 'general surgical' referral.

Results

Accuracy of diagnosis of SHOs in the accident and emergency department

Of 711 patients seen, no diagnosis was recorded for 70 (10 per cent) patients. An accurate diagnosis was made in 54 per cent of the remaining cases. If the 70 patients in whom no diagnosis was recorded are included in the series, the accuracy is 53 per cent.

Speciality of adviser called

All patients were admitted and there would therefore have been some consultation with an adviser. However, no record of this could be found in 122 (17 per cent) instances, indicating that these patients were probably discussed with an adviser by telephone. The adviser, in deciding not to come to the accident and emergency department, therefore accepted the SHO's assessment that the patient needed to be admitted. The remaining patients were seen in the accident and emergency department, 22 per cent by senior staff in that department, 55 per cent by doctors from general surgery, 17 per cent by a gynaecologist, 2 per cent by a urologist and 4 per cent by doctors from other specialities, usually medicine.

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* *F. T De Dombal, personal communication*

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Table 1 *Accuracy of diagnosis by accident and emergency senior house officers and their advisers*

	Accuracy of diagnosis (%)	
Sample	SHO	Adviser
Recorded diagnosis only	54·1 ($n = 641$)	62·7 ($n = 406$)
All cases seen	52 7 ($n = 711$)	55 4 ($n = 589$)

SHO, senior house officer

Table 2 *Agreement and disagreement in diagnoses of senior house officers and advisers*

	SHO's diagnosis		
Adviser's diagnosis	Correct	Incorrect	No diagnosis
Correct	167	69*	18*
Incorrect	38†	103	11†
No diagnosis or patient not seen	142	122	41

Values are numbers of patients; SHO, senior house officer; * adviser improved diagnosis of SHO, † adviser's diagnosis less accurate than SHO's

Accuracy of diagnosis by adviser

In 183 (26 per cent) cases, notes were made by the adviser but no diagnosis was recorded and, as noted above, no record was made in 122 patients. In all these cases, the adviser accepted the SHO's provisional diagnosis, or at least accepted that the patient needed to be admitted. In the remaining 406 patients accuracy of diagnosis was 63 per cent. If the instances where no diagnosis was recorded are included, the accuracy is 55 per cent.

Table 1 shows the accuracy of the SHOs and their advisers. Whether or not patients in whom no diagnosis was made are included, the advisers show only a slight superiority. It should be noted that these data do not constitute a formal comparison as the adviser did not see a proportion of the patients, and the incidence of no diagnosis being recorded is different in each group. However, if the analysis is restricted to the 377 cases where both SHO and adviser made a diagnosis, the results are similar: accuracy is 54 per cent for SHOs and 63 per cent for their advisers.

Effect of second opinion

A comparison of percentages can offer some indication of comparative diagnostic performance but it is more important to determine the direct effect on patient management. *Table 2* shows the diagnostic accuracy of both the SHO and adviser and hence also where they agree and where they disagree.

The diagnoses of the adviser and SHO concurred in 270 patients both being correct in 167 and both incorrect in 103 instances (*Table 2*). Clearly, the adviser had no major effect on the diagnosis of the SHO in these cases; nor did the adviser have any effect on diagnosis for those cases where he either did not see the patient or did not make a diagnosis. However, in the remaining patients, the adviser did have an effect on diagnosis In 69 cases the adviser corrected an inaccurate diagnosis by the SHO, and in 18 he made a correct diagnosis when the SHO had made no diagnosis. Thus in these 87 instances the adviser improved the diagnosis. In contrast, the adviser altered a correct diagnosis 38 times, and made an incorrect diagnosis, when the SHO had made no diagnosis, 11 times. Thus, in these 49 instances, the adviser's intervention produced a less accurate diagnosis On balance, therefore, the advisers improved the diagnosis of the 711 patients in only 38 (5 per cent) cases.

Accuracy of diagnosis by grade of advising doctor

In only 363 instances could both the grade of the adviser and the diagnosis he made be established. In the remainder there was some difficulty in tracing the grade, often because the adviser's signature was illegible or because the adviser was a locum of unknown grade. The junior doctors were, if anything slightly more accurate (SHOs, 61 per cent of 109 cases registrars, 59 per cent of 148 cases) than their more senior counterparts (senior registrars, 55 per cent of 106 cases) although the difference is not great; this may be partly explained by the SHO having more time to spend with the patient, or by the possibility that senior doctors were consulted about more difficult cases. Nevertheless, even fairly senior doctors appear to diagnose no more accurately on first presentation than accident and emergency department SHOs.

Accuracy of referral by senior house officers

The referral that the accident and emergency SHO would have made on the basis of his or her diagnosis was assessed in the manner described above; 682 patients were successfully classified in this way. In the remaining 29 patients no diagnosis or a diagnosis of non-specific abdominal pain, was made by the SHO and the patient was then seen by a senior accident and emergency department doctor. The referral that the SHO would have made could not, therefore, be established.

Table 3 compares the referral that the SHO would have made with the referral that would ideally have been made according to the final diagnosis. Thus it is a fairly stringent test of the accuracy of referral. The first column of the table shows that the SHOs would have referred 454 patients to a general surgery ward, 436 of whom would have been correctly referred and 18 incorrectly; 12 should have been sent to gynaecology 3 to urology and 3 to a medical ward. The other columns of *Table 3* are interpreted similarly.

In all, *Table 3* shows that 639 (94 per cent) patients would have been correctly referred by SHOs and 43 (6 per cent incorrectly referred. For the 43 errors of referral the decision of the adviser was also examined. In only 12 of these cases did the advisers correct a potentially inaccurate referral by the accident and emergency SHO.

Accuracy of referral by adviser

The referrals made by the advisers were examined in the same way as those for the SHO, i.e on the basis of their primary diagnosis. Of the 406 patients in whom a diagnosis was made, 383 (94 per cent) received a correct referral and 23 (6 per cent) received an incorrect referral: in 4 of these patients, the adviser altered a previously correct referral. In this group the accuracy of referral by the SHOs is also 94 per cent.

Overall, the adviser improved the referral in 12 instances and altered a correct referral in 4, thus improving the referral on only 8 occasions. This figure is only definitely established for the 406 cases where the adviser made a diagnosis. However, it seems reasonable to assume that in the remaining patients, where no record was made, the adviser did not improve on the SHO's

Table 3 *Accuracy of referral by senior house officers*

	Referral according to SHO diagnosis			
Speciality according to final diagnosis	General surgery	Gynaecology	Urology	Medicine
General surgery	436*	6	5	4
Gynaecology	12	122*	4	1
Urology	3	2	46*	2
Medicine	3	—	1	35*
Totals	454	130	56	42

Values are numbers of patients; SHO, senior house officer, * 639 correct referrals assessment. The advisers therefore improved the referral in only 8 (1 per cent) of the 711 patients studied.

Discussion

Doctors who advise accident and emergency SHOs were only slightly more accurate in their initial diagnosis of abdominal pain than the SHOs themselves. However, at this stage of patient management, making an exact diagnosis is not very important. Once the decision to admit has been made, the next major decision is where to send the patient. Here too the advisers contributed little to the immediate management of the patient. This study has shown that the SHOs are very accurate as regards the direction of referrals, with only 43 (6 per cent) patients being misdirected. The referrals of the advisers, when they record a diagnosis, also result in 6 per cent incorrect referrals. In only 12 instances did the advising doctor correct an erroneous referral, and in 4 he altered a previously correct referral. Thus, on balance, the adviser improved the referral only eight times (1 per cent). It should be stressed that in 17 per cent of cases there was no record of the adviser seeing the patient and in a further 26 per cent no diagnosis was recorded. Overall, therefore, the advisers contributed little to the immediate management of the patient.

We suggest that the adviser's role could be done as well on the ward. These results suggest that calling an adviser with authority to admit patients is an unnecessary and unproductive stage in patient management. The SHOs refer accurately in most cases and the admitting doctor on the ward will be able to redirect the few erroneous referrals that would previously have been picked up in the accident and emergency department. As it is, patients are kept waiting for the adviser, perhaps in considerable discomfort, for no very good reason; in some instances their condition may be worsening rapidly, and needlessly. It would seem more sensible for accident and emergency SHOs to take the decision to admit, at least in respect of acute abdominal pain. It is a curious paradox that the SHOs are not allowed to admit patients but are allowed to discharge a patient, a potentially much more dangerous decision. If accident and emergency SHOs were given the authority to admit a patient a regular audit would, of course, be necessary to ensure that the absence of a colleague's opinion did not lead to a lowering of standards. We also considered the extent to which the accident and emergency SHOs used the computer to assist their diagnosis. It appears to us that the computer is under-used and, when used, its recommendations may not be followed. Many previous studies have demonstrated the value of such systems. It seems likely that the proper use of the computer might be a quicker and more effective way of SHOs seeking advice.

This study has only assessed the diagnosis of admitted patients. It might be argued fairly that the advisers make a contribution by discharging patients who might otherwise be needlessly admitted. The majority of patients seen are admitted. The outcome of the discharged patient is not known; this would obviously be a valuable follow-up study, and would strengthen the argument for a direct admission process.

If accident and emergency SHOs took over the role of admitting officer, they would need training to carry this responsibility. We propose that the key decisions the SHO has to make are: first, whether to admit; second, whether to consider the condition as severe, and therefore urgent; and third, where to refer. Training should be primarily directed towards assisting the SHO in making these decisions. Making an exact diagnosis should be a secondary aim, and training in that skill should follow more basic training aimed at knowing when and where to admit.

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Effect of continuous postoperative epidural analgesia on intestinal motility

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The effect of postoperative epidural bupivacaine on intestinal motility was studied by measuring the transit time of barium contrast through the intestines in 16 patients after resection of the left colon and/or rectum. Fourteen patients served as controls and received postoperative injections of pentazocine. Mean transit time through the intestinal trac was 35 h in the epidural group and 150 h in the control group, a difference that is significant at the 0·1 per cent level. The average time before passage of flatus and faeces was different between the two groups a the 0·1 per cent level. We conclude that postoperative epidura bupivacaine constitutes an effective means of analgesia after colorecta surgery and is associated with a short duration of intestinal paralysis

Keywords: Intestinal motility, postoperative, epidural anaesthesia, colorectal surgery

Postoperative gastrointestinal paralysis is a significant problem in abdominal surgery[1–3]. Several studies have been performed in animals and man in attempts to elucidate the mechanisms of the inhibition of gastrointestinal motility[4–7].

Animal studies by Glise[8] suggest that there are different reflex mechanisms of gastrointestinal paralysis. An important finding in these studies was the presence of a non-cholinergic, non-adrenergic spinal reflex mechanism which leads to bulbar centres and which was resistant to pharmacological intervention. Spinal or epidural anaesthesia has been suggested as a means of inhibiting this pathway An anaesthesia level of about T6–8 has been proposed as adequate to abolish the inhibitory reflex mechanisms elicited by colorectal surgery[9].

The employment of epidural anaesthesia seems logical as this is a commonly used means of achieving postoperative analgesia involving the use of local anaesthetics and/or epidural morphine. There are conflicting opinions on the effect of these drugs on gastrointestinal motility[7,10–13].

The objective of the present study was to investigate whether continuous postoperative epidural bupivacaine shortens the duration of intestinal paralysis when compared with that of a postoperative regimen including intermittent injections of pentazocine, a benzomorphan derivative which in therapeutic doses does not decrease the propulsive activity of the intestines[14,15].

Patients and methods

Thirty patients admitted for surgery of the left colon and/or rectum were randomly allocated to postoperative epidural analgesia or intermittent injections of pentazocine (controls) Informed patient consent was obtained in all cases and the study was approved by the Regional Ethical Committee, University of Linkoping The number of patients, age distribution, diagnoses and operation procedures are given in *Table 1*. *Figure 1* shows the experimental design In the epidural group, an epidural catheter was inserted before operation at a level of L2–L3 The adequacy of the catheter placement was tested by injecting Carbocain® (Breon Laboratories, New York, USA) (2·5 mg ml^{-1}, 15–18 ml according to body weight) followed by assessment of the anaesthesia level About 1 h before termination of the operation, 6–8 ml of bupivacaine (2·5 mg ml^{-1}) were added to the general anaesthesia to secure adequate analgesia during the transport of the patient to the postoperative department

In both patient groups, a three-channel duodenal tube (gastric lumen, duodenal lumen, balloon lumen) was inserted during the operation with the duodenal lumen positioned in the ascending part of the duodenum One hour after the operation, 150 ml of barium were injected down the duodenal line and the transit time through the small and large intestines was investigated by serial X-ray examinations, the intervals being 4–6 h during the first postoperative day. If the transit of barium was not very fast, intervals between films were then prolonged to 12 or 24 h so as to reduce the X-ray exposure The radiological examination was stopped when the barium had reached the colostomy or had passed beyond the anastomosis and reached the distal rectum The use of this method also allowed assessment of the integrity of the anastomosis

After the operation, the epidural patients received intermittent injections of bupivacaine (2·5 mg ml^{-1} without adrenaline, 8–15 ml according to body weight and pain-relieving effect) for 48 h The controls were correspondingly given intermittent intravenous injections of 30–60 mg pentazocine according to the experimental protocol

Experimental procedure

All patients were managed postoperatively according to a strict protocol including assessment of the analgesic effect of the administered drugs every hour by assigning the following test points to the protocol· pain-free patient even when firm pressure was applied to the wound, no points, patient without pain at rest but with pain reaction when applying pressure on the wound, 1 point, patient complaining of pain at rest and with prompt reaction when touching the wound, 2 points. When the patient received pain points $\geqslant 1$, the respective analgesic drug was administered The intervals for and doses of bupivacaine were individualized to maintain an anaesthesia level of at least T8–10 during the first 24 h postoperatively The anaesthesia level was tested by using a spray with ethylene chloride.

Statistics

The Wilcoxon signed rank sum test for independent samples was used for comparison of the variables in the epidural and control groups

Results

Figure 2 indicates the average epidural anaesthesia level obtained during the first postoperative day for each of the 16

Table 1 *Characteristics of 30 patients who were randomly allocated to epidural or control group*

	Epidural group ($n = 16$)	Control group ($n = 14$)
Age (years)	46–75 (66)	53–75 (66)
Diagnosis		
Cancer of colon/rectum	13	11
Villous adenoma	2	3
Crohn's disease	1	—
Operation		
Rectal excision	6	8
Resection of rectum or sigmoid colon	10	6

Values in parentheses are the means

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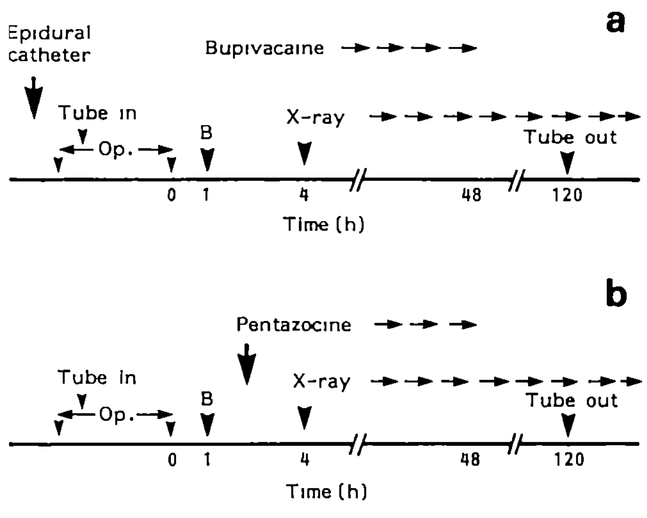

Figure 1 *Schematic illustration of the experimental design. Patients receiving epidural bupivacaine postoperatively had a catheter inserted before operation. The controls were given injections of pentazocine Transit time of barium through the intestines was determined by regular X-rays. B, barium; tube, duodenal tube. See text for details*

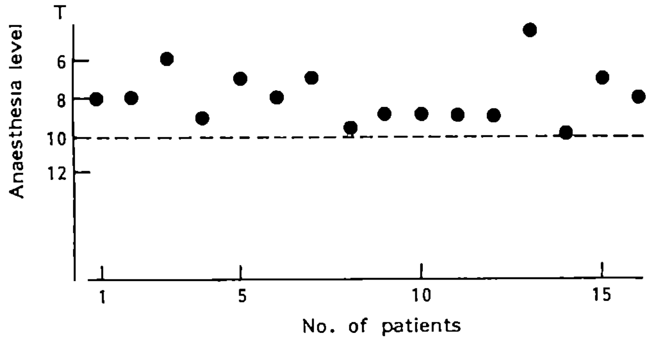

Figure 2 *Average anaesthesia level in the epidural group during the first postoperative day.* ---, *Lower limit of the desired anaesthesia level, T, thoracic level*

patients in this group. All patients had a mean level at or above T 10. Insertion of the epidural catheter was not accompanied by any complications. Varying degrees of muscular weakness of the lower limbs were regularly observed after epidural bupivacaine, only one of the patients considering this to be a disturbing factor.

To maintain optimal analgesia bupivacaine had to be administered every second hour. Correspondingly, the controls received pentazocine in doses between 60 and 180 mg during the first 24 h postoperatively. Assessment of pain relief during the first 24 h postoperatively according to our pain scale gave a mean score of 0·91 in the epidural group and 0·98 in the controls.

Figure 3 shows the transit time of barium through the small and large intestines The average transit time through the small bowel was 12 and 24 h in the epidural and control group, respectively, the difference being statistically significant at the 5 per cent level. The mean transit time through the entire intestinal tract was 35 h in the epidural group and 150 h in the controls, a difference that is statistically significant at the 0·1 per cent level. In the two subsets of operations, abdominoperineal excision of the rectum and anterior resection, there were no differences in caecal or total transit time in either the epidural or the control group.

The relationship between transit time and time to passage of flatus and faeces is shown in *Figure 4*. The average time before flatus or faeces was passed was obviously less in the epidural group than in the control group, but there was a high variability of the individual values in both groups as indicated by the wide variation in the standard deviation. The differences between the groups were significant at the 0·1 per cent level

No patient in either group showed clinical or radiological signs of anastomotic leakage.

Discussion

The present study describes postoperative management with continuous epidural analgesia. The controls were supervised

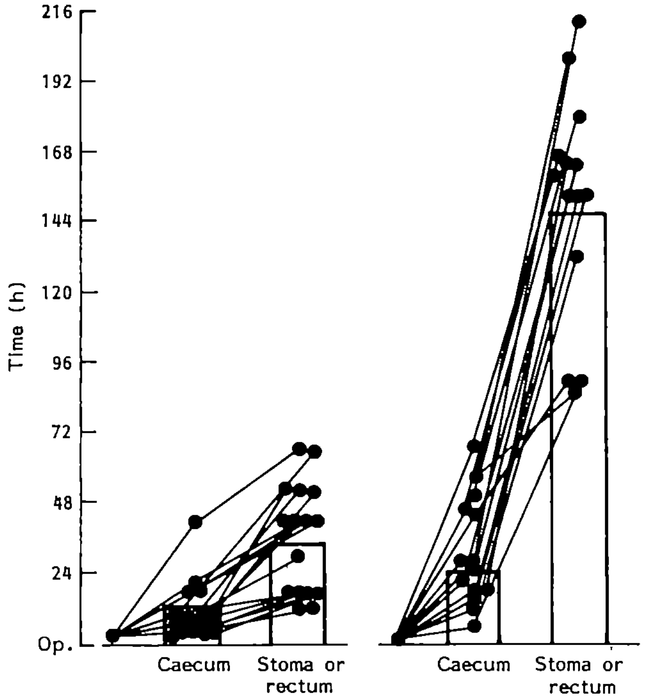

Figure 3 *Transit time of barium contrast from duodenum to caecum, and to sigmoidostomy or rectum. Histograms represent means Significant differences were observed between the epidural and control groups*

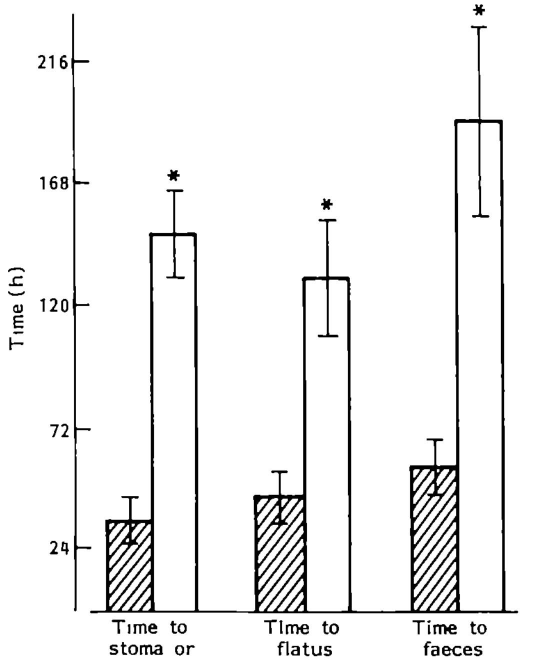

Figure 4 *Transit time of barium from duodenum to colostomy or rectum, and time to first passage of flatus and faeces. Histograms represent means. Significant differences were found between the two groups* ▨, *Epidural group,* ☐, *control group*

according to the same experimental protocol as the epidural patients. We chose pentazocine instead of the more commonly used opiates because, to our knowledge, no decreasing effects on intestinal motility have been reported, the possible increase in motility with high doses[14,15] being regarded as more acceptable for our experimental design.

Compared with the control group the transit time of barium contrast through the intestinal tract was significantly shorter when using the epidural modality and the same observation was made regarding time before passage of flatus. Bowel activity of the epidural patients was restored within the second postoperative day, indicating favourable conditions for early institution of enteral and oral nutrition. The risk of anastomotic disruption is a matter of debate when considering early restoration of bowel activity and especially when proposing early enteral and oral nutrition. In our study, no patient in either group showed signs of anastomotic leakage

We believe that this risk is highly exaggerated if satisfactory surgery is performed and if drugs stimulating peristalsis are avoided. A recent study by Johansson *et al.*[16] has shown that intra-operatively administered epidural bupivacaine increases blood perfusion of the colon, even in the anastomotic area. This observation indicates a beneficial situation for tissue proliferation and anastomotic consolidation in conjunction with epidural bupivacaine.

The mechanisms of the effect of epidural analgesia on intestinal motility were not studied by us A general sympatholytic effect has been proposed to be of major importance[17] According to our protocol, the same degree of postoperative analgesia was planned for both groups, and they achieved comparable pain scores during the first 24 h. Therefore, a superior pain-relieving effect of epidural analgesia was not confirmed in our study

The regularly observed muscular weakness of the lower limbs after epidural bupivacaine was considered to be a disturbing factor in the early postoperative period in only one patient. Regarding deep vein thrombosis, Modig *et al*[18,19] have shown a lower frequency of postoperative thromboembolism after epidural local anaesthetics compared with general anaesthesia A drawback of intermittent epidural bupivacaine is that frequent injections are needed to maintain the desired degree and level of anaesthesia. In the present study, bupivacaine had to be given every second hour, high total doses being administered in the early postoperative period We did not observe any adverse effects of this regimen, but a decreasing pain-relieving effect during the postoperative course was seen in two patients. We were able to avoid hypotensive periods by monitoring central venous pressure and carefully compensating for any blood or fluid deficiency Continuous epidural infusion of bupivacaine should be more convenient and perhaps allow the same analgesic effect using a lower total dose of the drug. This subject calls for further investigation

Epidural morphine is an alternative for postoperative analgesia with the advantages of longer effect and the absence of muscular weakness Morphine is a drug known to induce gastrointestinal inhibition and has the theoretical drawback posed by the risk of systemic effects[17] In a recent study performed in our department using the described protocol, epidural morphine given to 12 patients did not shorten the transit time of barium through the intestinal tract, the mean transit time being similar to that of the control group in the present study[13].

Our results differ from those reported by Cassuto[11] who did not find any beneficial effect of continuous epidural bupivacaine given during the first 24 h postoperatively, transit time being studied with radio-opaque markers. His study was carried out on cholecystectomized patients where long-standing gastrointestinal paralysis is an infrequent finding in our experience. Furthermore, there is much evidence that epidural analgesics with local anaesthetics affect the endocrine-metabolic response after lower abdominal surgery, whereas such an effect has not been demonstrated in upper abdominal surgery[5] Nielsen[12] used a combination of low doses of epidural bupivacaine and morphine in a large but unselected group of laparotomy patients. He did not observe any beneficial effect of the epidural modality when considering clinical signs only.

Our study was performed in conjunction with surgery on the left colon and/or rectum in an attempt to limit the surgical procedures under consideration and to include operations frequently associated with long-standing paralysis.

The present study shows that the transit time of barium contrast through the intestinal tract is significantly shorter after colorectal surgery when using postoperative epidural bupivacaine compared with intravenous injections of pentazocine. We conclude that epidural bupivacaine is an effective means of achieving analgesia after colorectal surgery with a short time of intestinal paralysis.

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Incisions with knife or diathermy and postoperative pain

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The severity of postoperative pain is influenced by numerous factors, such as anaesthesia, analgesia and technique of surgery—including the method of incision of tissues. To determine the effect of one such variable, we compared postoperative pain in patients having knife or diathermy incision of subcutaneous tissues during cholecystectomy.

Patients and methods

A total of 200 patients undergoing cholecystectomy were admitted to the trial and randomized by sealed envelopes into group A or B (*Table 1*). Randomization was restricted and stratified for sex giving equal numbers of men and women in each group. In group A, a scalpel was used for cutting. In group B, a scalpel was used for cutting the skin only; the remaining tissues were incised with cutting diathermy. Bleeding points were controlled by coagulation diathermy in both groups. An earth-free transistorized solid state diathermy generator was used. Both groups had a standard premedication and anaesthetic. Patients gave informed consent to participate; they were all undergoing cholecystectomy for chronic cholecystitis. Patients with chronic obstructive airways disease and those requiring choledochotomy were excluded. No analgesia was given for 24 h before the trial which ended 24 h after the operation. Four consultant surgeons participated using identical surgical technique. Kocher's incision was used in all patients. Group identity was inevitably known to the operating surgeon but he was not involved in the postoperative assessment during the trial period.

On demand morphine (0·15 mg/kg body weight) was given parenterally for postoperative pain and the amount consumed was used as one of the indices of severity of pain. The patients scored a visual analogue sheet as a measure of severity of pain on a 10 cm scale (no pain to worst imaginable pain) at 4-hourly intervals. Peak expiratory flow rate (PEFR) was recorded as a best of three blows through a Wright's peak flow meter, pre-operatively and at 18 and 24 h postoperatively. Data were analysed by the Mann–Whitney *U* test; values of $P<0.05$ were considered significant.

Table 1 *Clinical details of patients in the trial*

	Male	Female	Age in years (range)	Age in years (mean)
Group A	16	84	28–56	35
Group B	16	84	26–54	37

Group A, scalpel incisions, group B, diathermy incisions

Results

Results of the visual analogue pain scale showed a wide range of values at each time period (*Table 2*). There were significantly smaller pain scores reported in group B patients as compared with group A patients. There was a statistically significant difference in PEFR at 24 h postoperatively between the two groups ($P<0.05$), but not at 18 h postoperatively ($P>0.05$; *Table 3*). Group B patients demanded fewer morphine injections and required less total analgesia than group A patients during the trial period (*Table 4*).

Discussions

In measuring pain patients may be unreliable and inconsistent[1]. Subjective measures such as a linear visual analogue scale and objective measures such as PEFR are useful in postoperative pain measurement[2–5]. More pain is experienced from the parts of the body that move constantly, such as the chest and abdomen[6]. Cholecystectomy was chosen as a model because it is

Table 3 *Peak expiratory flow rate as a measurement of pain*

		Time after operation	
	Pre-operative	18 h	24 h
Group A	3·50 (2·82–4·52)	1.52 (1·35–1·75)	1·60 (1·32–1·88)
Group B	3·61 (2·92–4·42)	1·64 (1·42–1·85)	2·1 (1·6–2·2)
P^* ($n=100$ pairs)	>0·05	>0·05	<0·05

The mean (range) peak expiratory flow rate is given in litres/s. Group A, scalpel incisions; group B, diathermy incisions. *Mann–Whitney *U* test, group A *versus* group B

Table 4 *The requirement for morphine in the postoperative period*

	Mean	Range
No. of times an injection of morphine was required in 24 h		
Group A	5	3–6
Group B	3	2–5*
Milligrams of morphine injected in 24 h		
Group A	52	30–60
Group B	30	20–52*

Group A, scalpel incisions, group B, diathermy incisions, *Mann–Whitney *U* test $P<0.05$ ($n=100$ pairs), group A *versus* group B

Table 2 *Results of the assessment of postoperative pain using the visual analogue scale*

	Time after operation				
	4 h	8 h	12 h	16 h	24 h
Group A	5·75 (2·7–8·5)	8·85 (6·0–10·0)	6·75 (1·0–8·3)	3·80 (3·0–5·0)	6·75 (0·7–8·3)
Group B	3·85 (1·0–6·0)	5·92 (2·3–9·6)	4·36 (0·7–7·5)	3·0 (1·0–5·0)	4·35 (0·7–7·7)
P^* ($n=100$ pairs)	<0·02	<0·01	<0·02	<0·01	<0·02

Mean (range) scores are given. Group A, scalpel incisions, group B, diathermy incisions. * Mann–Whitney *U* test ($P<0.05$ considered significant), group A *versus* group B. The visual analogue scale ranges from 0 to 10 cm

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a common operation on the upper abdomen. Many reports suggest that the treatment of postoperative pain is inadequate[7–16]. Several studies have compared the effect on postoperative pain of different analgesic and anaesthetic techniques[16–20]. In contrast, there are few studies on the effect of pain using different surgical techniques.

A delta fibres are involved in the generation of sharp pain and C fibres in the generation of dull persistent pain. Depending on the strength of stimulation or the pattern of coding of neural impulses, other sensations can be perceived as pain[21]. Diathermy burns the nerves in the process of cutting. A knife on the other hand only divides tissue. Both cause postoperative pain but burning while cutting may cause less pain. This situation may be similar to third degree burns which are anaesthetic. Partial burning around the edges accompanying any thermal injury would be painful but the severity of pain appears to be less than after cutting. In conclusion, cutting diathermy may be superior to the knife in making incisions less painful.

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Techniques for better suturing

Suturing techniques enhancing the accuracy of suture placement and reducing the forces on the tissue being sutured were evaluated in six surgeons, each with 6 years' surgical experience. The accuracy was assessed by the distance between the actual and designated needle exit sites. Force was expressed in terms of the torque on the needle holder using a maximum of the torques (max. F*), maximum derivative (*dF/dt*) and integral (*IF*). The effects of four factors (suturing techniques) on suturing were evaluated: (1) placement of the needle holder on the needle; (2) inclining the tissue at needle entrance, as is commonly done by elevating with forceps (unnoted role of the forceps); (3) adjustment of the needle's exit during suture placement, as is unknowingly employed in practice, and (4) variation between individual surgeons. All these factors affected the accuracy and force of suturing. Gripping the needle closer to the tip strongly reduced the max.* F, dF/dt, *and* IF *per time, as did inclining the tissue. Adjustment of exit improved accuracy, but has the potential for causing avoidable tissue injuries. Differences between surgeons suggest the necessity of addressing fundamental surgical techniques and formally incorporating them into the training programme.*

Keywords: Operative technique, suturing technique, needle grip, forceps

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The quality of the basic techniques of surgery, such as suturing or tying, has rarely been discussed in the surgical literature. Thus, not only is the effect of their quality on the outcome of operation unknown, but neither has a methodology for qualifying techniques been established. This study reports on the status of the surgeon's suturing techniques as assessed from two aspects: (1) the accuracy of suture placement; (2) the suture-related forces on, or trauma to, the tissue being sutured.

Materials and methods

Six surgeons, each with 6 years' surgical experience, attempted to produce a suture span of 2 cm which was marked on a paper with designated entrance and exit points. The paper was fastened to a urethane foam block (20·0 × 20·0 × 7·5 cm) The needle which was used was a half-circle cutting needle with a diameter of 29 mm, thus producing the theoretical span of 2 cm (References 1, 2) and the needle holder was a Hegar-type 18 cm in length Foam with the tactile qualities of living tissue was selected as the tissue simulant but required a maximum force, to drive the needle through it, five times as great as that required for fresh canine liver. Accuracy was assessed by measuring the distance between the actual exit site and the designated exit site, in millimetres The forces on the tissue being sutured were estimated based on the torque (F) on the needle holder F was measured by an isotonic transducer mounted in a holder (rotary differential transformer type, Model TD-112S, Nihon Kohden, Tokyo, Japan) (*Figure 1*) Its derivative (dF/dt) and integral (IF) were derived by Models ED-601I and EI-601G, Nihon Kohden, and recorded by a heat-writing recorder with a paper speed of 25 mm s^{-1} The following were employed as quantifiable variables to assess the suturing: (1) distance deviated (mm); (2) maximum F (kg cm); (3) maximum dF/dt (kg cm s^{-1}), (4) IF (kg cm s), (5) IF/T (g cm) and (6) time (T) (s)

The following technical factors were evaluated for their effect on suturing; (1) positioning of the needle holder on the needle (gripping), short or long, (2) inclining (sloping) the tissue (simulant) at the needle entrance; (3) adjusting the needle exit (wavering the needle in tissue), and (4) variation between individual surgeons. The needle was gripped by the holder at right angles 5 mm from the end (long grip) or 15 mm from the end (short grip) The urethane foam remained flat or was sliced obliquely at an angle of 45 degrees at the needle entrance (inclined) Suturing was attempted in one of two ways: either, the surgeon was permitted to move the needle from side to side to adjust its exit after it was introduced, as is the common practice, or he was not allowed to do so. Each variable was also compared for each of the six surgeons on an individual basis

The six surgeons attempted ten suturings for each of the eight possible variations (settings) of suture techniques (*Table 1*), and the effect of the technical factors was evaluated for each variable (*Table 2*)

The order of the settings was determined randomly The determinacy was evaluated by a four-way analysis of variance (ANOVA) with a replication of 60 for each variable. Differences between two corresponding settings were analysed by a paired mean test The difference between the surgeons was determined for each variable by a one-way ANOVA. Overshooting of suturing in suture placement was evaluated by the Fisher exact test

Results

The mean values for all the variations (settings) of suturing technique for all the surgeons (60 suturings) are listed in *Table 1*.

The effect of the four factors on suturing was derived by the ANOVA (*Table 2*). Position of the needle holder (gripping) affected all the variables except for IF Inclination had an effect on all except T, and adjustment affected all except maximum F and dF/dt. The technique of the individual surgeons affected all variables.

The paired mean test indicates that the short grip gave rise to significantly less deviation in suture placement, i.e. it gave

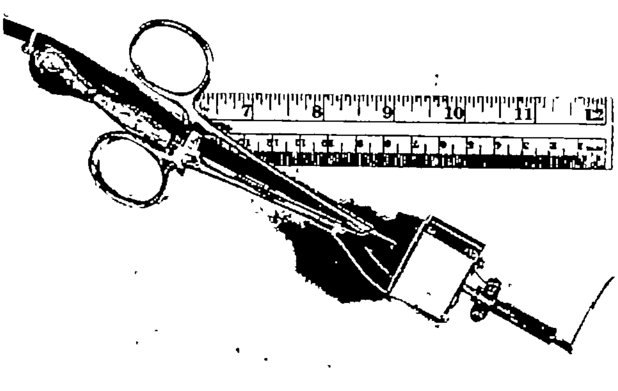

Figure 1 *Needle holder for measuring torques An isotonic transducer of the rotary differential type is positioned between the legs of the holder and is balanced by a lead weight*

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Table 1 *Means and ranges of variables used to evaluate the technical factors of suturing*

	Short grip				Long grip			
	No inclination		Inclination		No inclination		Inclination	
Variables	No adjustment	Adjustment	No adjustment	Adjustment	No adjustment	Adjustment	No adjustment	Adjustment
Deviated distance (mm)	2·6±1·6 0·5–7·1	1·3±0·8 0·0–3·2	1·5±1·1 0·0–5·1	0·9±0·8 0·0–3·6	2·9±1·7 0·0–8·0	1·4±1·1 0·0–4·5	2·2±1·4 0·0–5·0	1·3±1·1 0·0–5·5
Maximum torque (F) (kg cm)	0·78±0·42 0·15–2·00	0·85±0·38 0·15–1·70	0·46±0·26 0·10–0·90	0·60±0·31 0·10–1·30	1·08±0·32 0·50–1·80	1·00±0·34 0·45–1·90	0·95±0·35 0·40–2·70	0·70±0·30 0·15–1·75
Maximum dF/dt (kg cm s^{-1})	2·69±1·32 0·75–6·25	2·69±1·15 0·75–5·25	1·98±1·21 0·50–6·50	2·49±1·25 0·50–5·50	4·20±1·53 1·75–8·25	3·88±1·36 2·00–8·00	3·40±1·35 1·75–6·75	3·23±1·28 1·00–6·25
Integral of F. (IF) (kg cm s)	0·39±0·29 0·10–1·15	0·64±0·45 0·15–2·40	0·21±0·13 0·05–0·65	0·48±0·45 0·05–2·20	0·40±0·14 0·15–0·80	0·59±0·25 0·25–1·80	0·40±0·23 0·15–1·50	0·40±0·15 0·15–0·70
IF/Time (g cm)	159±78 58–333	170±75 54–354	100±40 34–203	116±58 21–256	198±61 91–325	200±65 90–407	193±76 74–469	136±43 67–280
Time (s)	2·3±0·7 1·1–3·6	3·6±1·2 2·2–7·6	2·0±0·6 1·1–3·3	3·7±1·8 1·4–8·6	2·0±0·4 1·4–3·2	3·0±0·8 1·7–7·2	2·1±0·6 1·0–3·6	2·9±0·7 2·0–5·0

Means with s.d. and ranges (minimum to maximum) of 60 suturings (10 each by 6 surgeons)

Table 2 *Effect of the technical factors of suturing on quantifiable variables*

	Variables					
Factors	Distance deviated	Maximum torque (F)	Maximum dF/dt	Integral of F (IF)	IF/T	Time (T)
Position of needle holder	Yes (0·001)	Yes (0·000)	Yes (0·000)	No (0·346)	Yes (0·000)	Yes (0·000)
Inclination	Yes (0·000)	Yes (0·000)	Yes (0·000)	Yes (0·000)	Yes (0·000)	No (0·322)
Adjustment	Yes (0·000)	No (0·525)	No (0·932)	Yes (0·000)	Yes (0·048)	Yes (0·000)
Variation among surgeons	Yes (0·000)	Yes (0·000)	Yes (0·000)	Yes (0·000)	Yes (0·000)	Yes (0·000)

Effect on the variables was assessed by a four-way ANOVA with replication of 60 (10 suturings each by 6 surgeons), P values are given in parentheses

greater precision, regardless of adjustment, compared with the long grip when the urethane was inclined (*Figure 2*), and the max. F, dF/dt and IF/T also were less with the short grip (*Figures 3–6*). IF was less only in the setting with inclination and without adjustment. T was shorter with the long grip in all the settings except those with inclination and without adjustment. Thus, generally, the short grip enhanced accuracy and reduced the force produced.

Inclination reduced the maximum F in all the settings, and also reduced the distance deviated, max. dF/dt, IF and IF/T in all but one. Thus, inclination helped to improve the suturing.

Adjustment of the needle exit shortened the distance deviated in all settings but increased IF in all but one; T was prolonged in all settings. The effect of adjustment on maximum F, dF/dt and IF/T was not consistent. Thus, adjustment enhanced accuracy.

Individual differences between surgeons in the deviated distance were significant in all but one setting, and affected all the settings of all the variables relating to force. T also differed in all settings but one. Thus, the surgeons used quite different techniques for suturing.

Suturing without adjustment overshot and undershot the designated exit in 49 and 8 out of 60 suturings (82 per cent and 13 per cent) using the short grip, and in 48 (80 per cent) and 7 (12 per cent) with the long grip when the tissue simulant was not inclined at the needle entrance; however, overshoot was reduced to 41 (68 per cent) and 40 (67 per cent), respectively, when the tissue simulant was inclined. Undershooting occurred in 8 and 15 suturings. In total, there were 97 instances of overshot suturing in the flat simulant and 81 in the slanted simulant, a significant difference ($P = 0·03$). Thus, the suturing tended to overshoot but inclination of the tissue reduced this tendency.

Discussion

In practice it is not uncommon for a needle to miss an intended exit site. Occasionally the tissue being sutured is heavily distorted or even torn by the needle's movements. Nevertheless, a detailed description of an ideal technique for suturing, to our knowledge, has never been offered in surgery—in fact, its clinical importance has not even been documented. However, the author believes that no surgeon will deny the importance of good suturing technique. In the present study the ideal result was assumed to be precisely placed sutures producing minimal distortions of, or trauma to, the tissue. To assess the accuracy of suture placement, the distance between the actual needle exit site and the designated exit site was measured, and the distortion was expressed as the force working on the needle holder. In previous studies suture placement has been shown to be less precise than many surgeons expected[1–3]. The present study is the first to have measured the forces involved in suture placement; further investigations are necessary before a complete analysis can be presented. For instance, the tolerances which allow suturing of the different organs in their normal state and in different stages of inflammation without traumatic injury need to be determined. The forces at work on the tissue, not on the needle holder as measured in the present study, should be measured. The forces produced while pulling a needle out of the tissue should also be determined. Some surgeons distort the

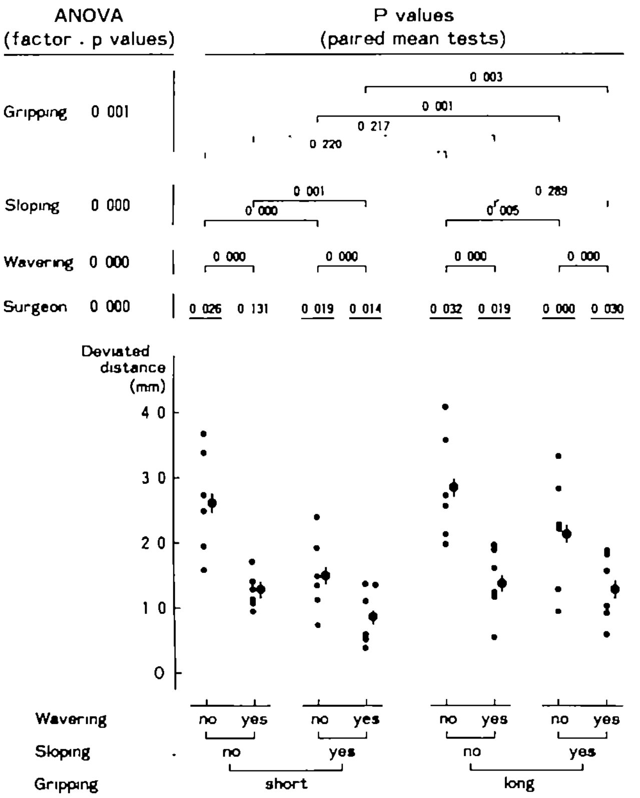

Figure 2 *Deviation distances The effect (determinacy) of the four factors on accuracy of suturing was evaluated by a four-way ANOVA, (gripping; sloping, wavering, surgeon) and the difference between two settings of suturing by a paired mean test* ●, *the mean of ten attempts by each surgeon;* ⧫, *the overall mean+s.d. of 60 attempts*

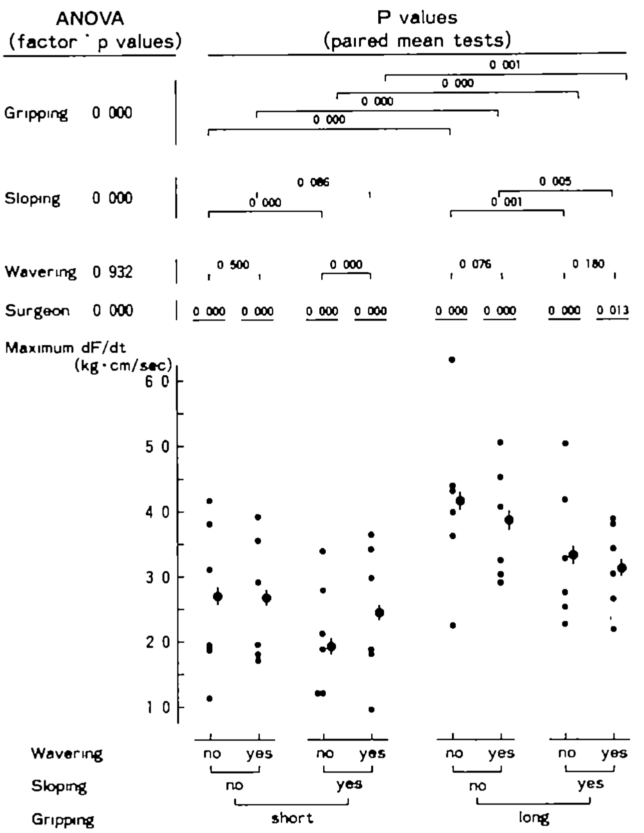

Figure 4 *Maximum derivatives of torques (dF/dt).* ●, ⧫, *as in* Figure 2

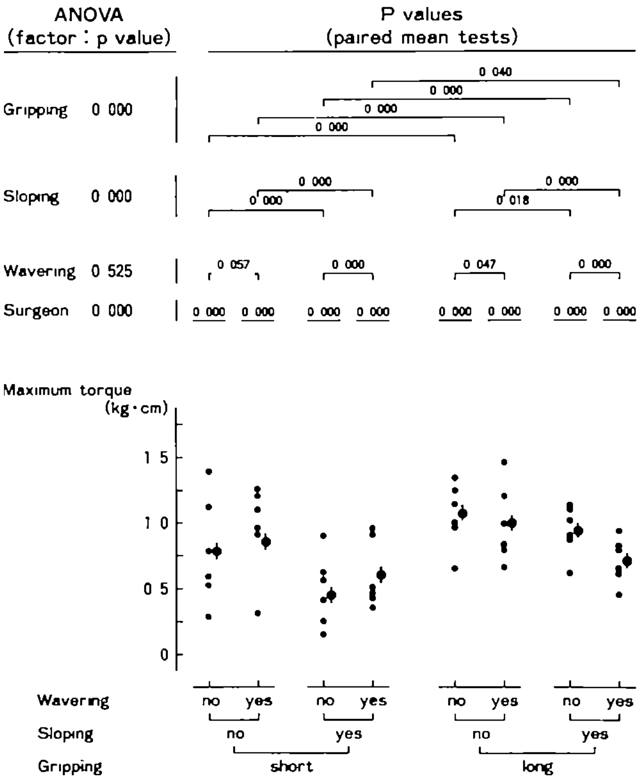

Figure 3 *Maximum torques* (F) ●, ⧫, *as in* Figure 2

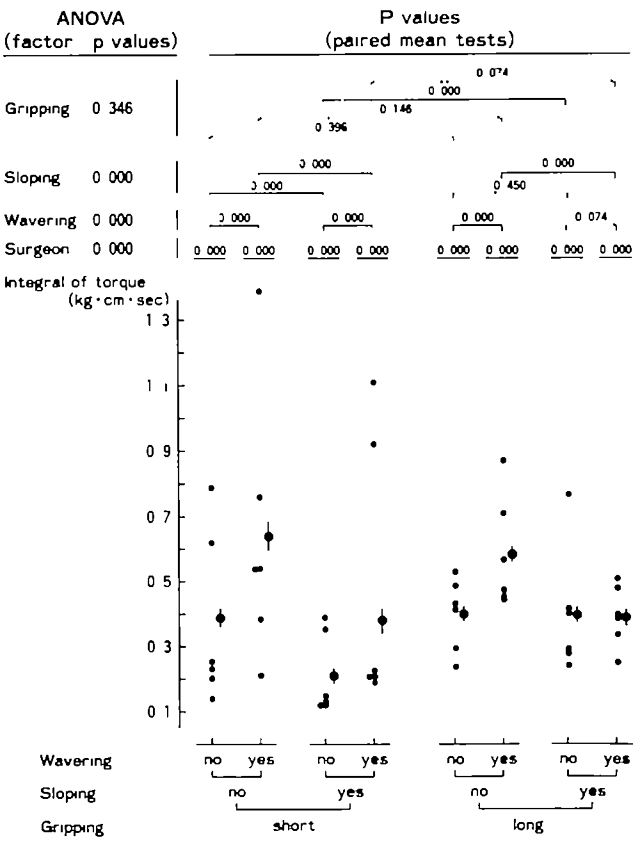

Figure 5 *Integrals of torques* (IF) ●, ⧫, *as in* Figure 2

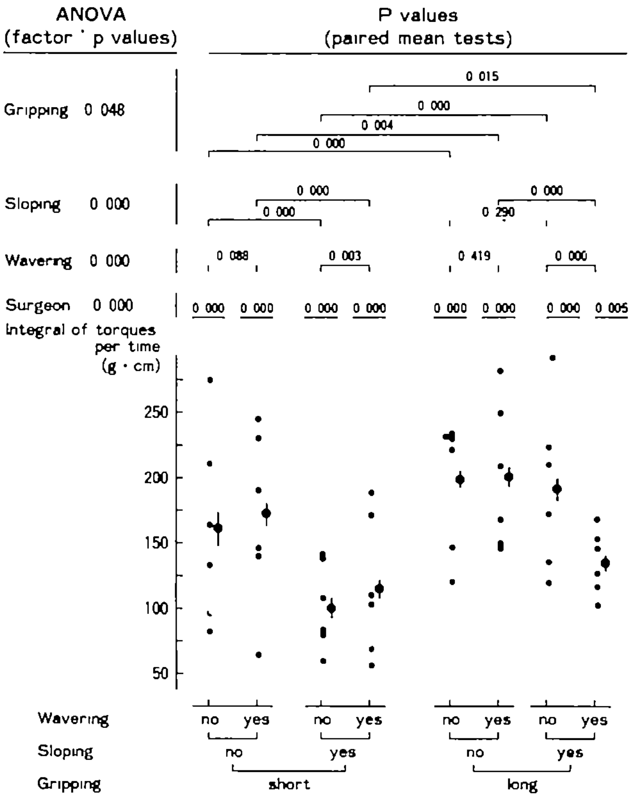

Figure 6 *Integrals of torques per time* (IF/T) ●, ⧫, *as in* Figure 2

tissue more severely when releasing a needle from a holder than when suturing the tissue. However, the results of this study are sufficient to make surgeons aware that careless technique inadvertently produces forces which are capable of causing serious injury to the tissues.

Although adjustment of the needle's exit site within the tissue to achieve precision in suture placement is a common technique, it injures the tissue. In critical sutures, in a vessel wall for instance, a needle hole produced by adjusting the needle may cause leakage.

The angle of the tissue at the needle entrance was shown to have a marked effect. When the forceps grasps the tissue to immobilize it for suturing, it also lifts it, making two entrance angles of the needle to the tissue, one for the tissue at the entrance and the other for the overall tissue. Then, even if the angle at the entrance is steep, there is less tendency to drive the needle more deeply into the tissue than intended, because the entrance angle to the inclined tissue is the sum of the angle of the tissue inclination and the entrance angle to the overall tissue. On the other hand, the suture span is proportional to the entrance angle to the overall tissue in ideal suturing i.e. the needle traces an arc which has a diameter equal to the needle's curvature. In our previous study[1] where the movement of the needle was free to deviate from the arc as a sheet of paper was the tissue simulant, 324 out of 462 sutures (70 per cent) overshot the designated exit, meaning that the entrance angle was too large. In the present study, going off course was restricted because the simulant was urethane foam. In the flat simulant 97 out of 120 sutures overshot, whereas 81 overshot in the slanted simulant, a significant difference ($P = 0{\cdot}03$). Thus tissue inclination at the point of entrance acts to lessen the effect of the large entrance angle and, thus, to improve the suturing technique.

Gripping affects both the force and accuracy of suturing; however, a significant increase in accuracy with the short grip occurred only when the simulant was inclined. The short grip decreases pronation of the forearm necessary to insert the needle. In the setting of the present study the initial position of the holder was 205 degrees to the simulant for the long grip (5 mm from the end) with an entrance angle of 45 degrees and was reduced to 166 degrees for the short grip (15 mm). Thus the track of the needle was less likely to deviate from the needle's arc as the initial position of the needle holder ($\leqslant 180$ degrees) was produced only by pronation of the forearm without involving other movements of the wrist and shoulder joints However, some surgeons increased the angle of entrance by re-utilizing pronation with the short grip, resulting in overshooting. As demonstrated in the previous and present studies[1–3], surgeons prefer to introduce a needle with a larger angle. According to the author's observations, in practice experienced surgeons unconsciously suppress pronation with the short grip, resulting in better suturing, whereas less experienced surgeons re-utilize that pronation to increase the entrance angle. Thus, the way that a needle is gripped apparently depends upon the surgeon's ability. However, the effect of the large entrance angle is lessened by lifting the tissue with forceps as previously discussed; this may account for enhanced accuracy achieved with the short grip when the simulant was inclined.

The author has noted that in practice each surgeon has a different level of technical surgical skill. The present study demonstrates how such differences may be quantified as effects on the variables measured in this study. These differences are so great that some assessment of technical ability should be included as a requisite for qualification as a surgeon.

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Treatment of Crohn's disease in relapse with cyclosporin A

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It has been suggested that cyclosporin A might be of some benefit to patients with Crohn's disease. The clinical response and side-effects of cyclosporin A in Crohn's disease are described in a series of 13 adults. The majority of patients had ileal disease and all but one were started on an initial oral dose of 15 mg/kg per day. Duration of treatment ranged from 3 to 42 weeks. Of the 13 patients, 6 showed a response to therapy; the remainder showed no response or deteriorated. The commonest side-effect was hyperaesthesia, but one patient developed nephrotoxicity and one developed hepatotoxicity. Significant drug malabsorption occurred in one case. The side-effects were dose dependent and reversible. Cyclosporin A may have a part to play in the treatment of resistant Crohn's disease, and in our hands has been associated with a 46 per cent response rate; however, the precise role of cyclosporin A in the management of Crohn's disease awaits further study.

Keywords: Crohn's disease, cyclosporin A

The primary treatment for Crohn's disease is medical, except where complications necessitate recourse to surgery. The mainstay of medical treatment is steroids, with the occasional need for azathioprine. These agents are immunosuppressive, and cause a non-specific down-regulation of the immune system. Cyclosporin A is a fungal peptide first described by Borel[1], and is a patent immunosuppressive drug. Its mechanism of action is not fully understood but it is thought to inhibit the release of interleukin-2, which is responsible for the clonal expansion and proliferation of antigen-specific T cells Cyclosporin A is specific for T lymphocytes which are numerous within the pathological lesions of Crohn's disease[2]. Thus there is a sound theoretical basis for its use in the management of Crohn's disease.

Patients and methods

Patients

Thirteen patients have been studied. Their ages ranged from 18 to 63 years, and their clinical details are summarized in *Table 1*. All patients had normal renal function, and in each case Crohn's disease was confirmed by endoscopy, radiology or biopsy. Active disease was determined by a Harvey–Bradshaw index (see below) of >4, and/or an ESR of >25 mm/h, haemoglobin <11 g/dl, albumin <35 g/l or elevated α_1 acid glycoprotein levels. Oral prednisolone of less than 10 mg/day was allowed but discontinued over the first week Written consent was obtained from the patient

Assessment of disease activity and treatment failure

The Harvey–Bradshaw index has been used to define active disease[3], but because of shortcomings in this method alone, haematological and biochemical criteria were included. Treatment failure was divided into three categories (A) failure to control the initial disease activity at the outset of the study, (B) worsening parameters of active disease; (C) the development of complications requiring surgical intervention Patients were reviewed at 2-week intervals for the first 8 weeks, and thereafter at 6-week intervals

Results

Of the 13 patients, 6 have shown some response to treatment with cyclosporin A (*Table 2*): 4 of these 6 have received treatment for >6 months, and 2 of these patients remain well with no recurrent symptoms, 1 having now remained free of recurrent disease for 12 months after cessation of the drug Two of the responding patients had late relapses while on maintenance therapy: one responded to dose escalation, but the other did not and required surgical resection of a small bowel stenosis Two further patients responded well to cyclosporin A, but had to stop treatment because of pregnancy in one case and hepatotoxicity in the other. The remaining seven patients showed no response to therapy, or worsened on treatment. Three patients were completely non-responsive to therapy (treatment failure category A), two patients worsened on

Table 1 *Details of patients with Crohn's disease treated with cyclosporin A*

Patient no	Age (years)	Sex	Disease extent	Previous surgery
1	24	F	Terminal ileum, perianal	Yes
2	36	F	Small bowel	Yes
3	18	F	Small bowel	No
4	53	M	Total small bowel, perianal	Yes, but inoperable
5	37	F	Terminal ileum	Yes
6	20	F	Terminal ileum, colon	No
7	22	M	Small bowel	No
8	31	M	Terminal ileum, perianal	No
9	63	F	Small bowel	No
10	26	F	Terminal ileum, colon	Yes × 3
11	37	F	Terminal ileum	Yes
12	28	M	Terminal ileum, colon	Yes
13	40	M	Small bowel, colon	Yes

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Table 2 *Patient outcome*

Response	Patient no.	Duration of treatment (weeks)	Comment
Yes	1	8	Responded, became pregnant
	2	32	Good response
	3	32	Very good response
	4	38	Good initial response, late failure due to nephrotoxicity
	5	47	Good initial response, late failure requiring hemicolectomy
	6	3	Good response, hepatotoxicity
No	7	4	No response, improved on steroids
	8	2	Worsening symptoms, intra-abdominal abscess
	9	8	No response, improved on steroids
	10	4	Worsening on treatment, improved on steroids
	11	4	Worsening on treatment, malabsorbed drug
	12	12	Questionable response, subacute obstruction, required surgery
	13	8	No response, improved on steroids

Table 3 *Causes of failure of treatment of Crohn's disease with cyclosporin A*

Patient no.	Cause of treatment failure
7	Non-responsive mucosal disease, no stricturing
8	Intra-abdominal abscess, probably present before study
9	Non-responsive mucosal disease, hypoproteinaemia
10	Non-responsive mucosal disease, no stricturing
11	Non-responsive mucosal disease, no stricturing
12	Small bowel stenotic lesion, required surgical resection
13	Non-responsive mucosal disease, no stricturing

treatment (category B), and two required surgical intervention (category C).

Causes of treatment failure

In most cases, the reason why patients failed to respond to cyclosporin A or worsened on treatment is not clear. Four of the patients had non-responsive mucosal disease with no evidence of stricturing; one of these was associated with significant hypoproteinaemia. In only three of the cases was there an obvious reason for treatment failure: in the first case, the patient was found to have extensive intra-abdominal sepsis with abscess formation which required surgical treatment, in the second case, there was a significant degree of intestinal obstruction which required surgical resection. Clearly, neither of these patients would have been responsive to any medical treatment and might have been more suitable for surgical intervention in the first place. In the third case with an identifiable cause for treatment failure, the patient never achieved serum cyclosporin A levels above 20 ng/ml (probable therapeutic range 150–200 ng/ml by radioimmunoassay). Despite the latter, it appears unlikely that the lack of response in seven cases is attributable to drug malabsorption as the serum drug levels in this group were higher than those in the responding group (*Figure 1*).

Indices of activity during therapy

Changes in haematological and biochemical parameters are shown in *Figures 2–4*. In the responding patients, the values shown are at weeks 0 and 6, but in the non-responders, the final values represent those at the time that therapy was discontinued (see *Table 2* for details). In all the responding patients, both the α_1 acid glycoprotein levels and the Harvey–Bradshaw index fell during therapy but no such trend was seen in the non-responding group, in which there were higher levels at the end of treatment for all patients except two (*Figure 2*).

Differences in the haemoglobin values were less obvious. The responding patients tended to maintain their haemoglobin levels, but they fell in all of the non-responders with only one exception. As expected, the non-responding patients tended to be more anaemic at the end of therapy, than those whose disease improved. The ESR fell in the majority of the responding patients, and rose in all of the non-responding ones (*Figure 3*). In one case in the responding group the ESR failed to fall, and rose to very high levels: this was the patient with hepatotoxicity, which may have been the cause of the raised ESR as the Crohn's disease was quiescent. The serum albumin levels are shown in *Figure 4*, and were higher in the responding patients at 6 weeks compared with the non-responders. At the outset of therapy the two groups were comparable, and had no significant differences in the median values of any of the above parameters.

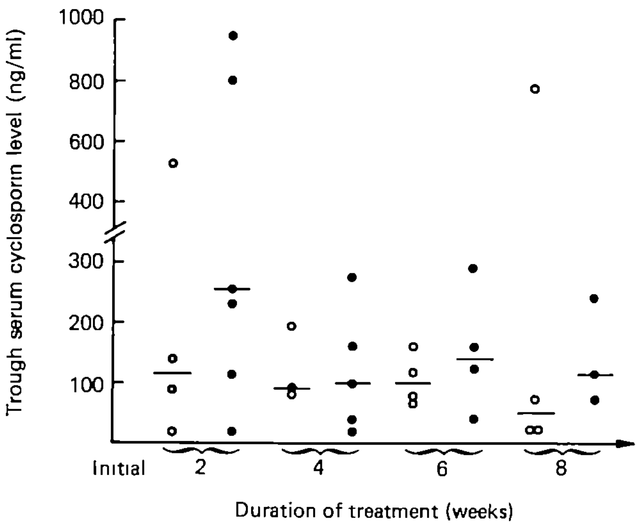

Figure 1 *Comparison of trough cyclosporin levels in responding* (○) *and non-responding* (●) *groups. Blood was collected 12 h after dose administration.* —, *Median value*

No statistical comparison has been made between the responders and non-responders because the two groups would be expected to have different values for such factors as ESR, activity index and haemoglobin level, as these indices were used to define response to therapy.

Adverse effects of treatment

Hyperaesthesia was the single most common side-effect and was seen in 11 of 13 cases (85 per cent). In one of the severe cases, nerve conduction studies were normal. One patient developed hepatotoxicity after 3 weeks' therapy (bilirubin 95 μmol/l; AST 142 units/l; alkaline phosphatase 282 units/l; normal ranges 1·7–17, <37, and 30–130 respectively). This occurred in association with a toxic serum level of cyclosporin A

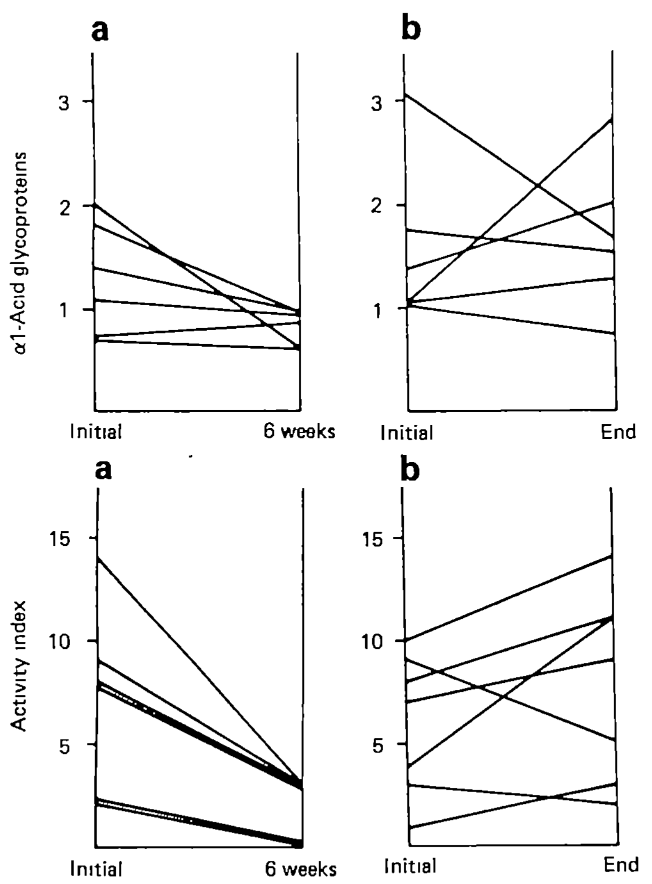

Figure 2 *Changes in Crohn's disease parameters during cyclosporin treatment: comparison of* **a** *responders,* **b** *non-responders*

(950 ng/ml). Serological studies for hepatitis A and B gave negative results, as did autoantibody tests. Liver biopsy showed a mild mixed cellular infiltrate, with slight prominence of Kupffer cells, and mild cholestasis. The appearances were thought to be consistent with a drug aetiology. One patient developed nephrotoxicity late in the course of treatment, with a serum creatinine level of 166 μmol/l. Patients in both groups had increased serum creatinine levels, as shown in *Figure 4*, but none were outside the normal range for our laboratory. Hypertrichosis was seen in three patients (23 per cent), gum hypertrophy in one (8 per cent), and tremor in three (23 per cent). All of the adverse effects were dose dependent and reversible.

Discussion

The use of cyclosporin A to treat Crohn's disease is not new. Allison and Pounder reported the first case in 1984[4], and a subsequent report by Bianchi *et al.* confirmed the earlier observation[5]. More recently, Allison and Pounder have reported a series of eight patients with Crohn's disease, seven of whom responded to treatment with the drug[6]. The drug has also been used with success in ulcerative colitis[7]. In the present study of 13 patients, 6 have shown a clinical response to therapy with cyclosporin, a response rate of 46 per cent. Indeed, since the drug was withdrawn from the patient with hepatotoxicity, it might be more accurate to say that the success rate is only 38 per cent (5 out of 13). It is not clear why only some of the patients have responded, as the disease activity was similar in the two groups of patients and serum cyclosporin levels were slightly higher in the non-responding group. The bioavailability of the drug has been very variable in patients with Crohn's disease, and serum levels appear to be much lower than those achieved with similar doses in renal transplantation. The latter problem might be prevented by the early use of intravenous

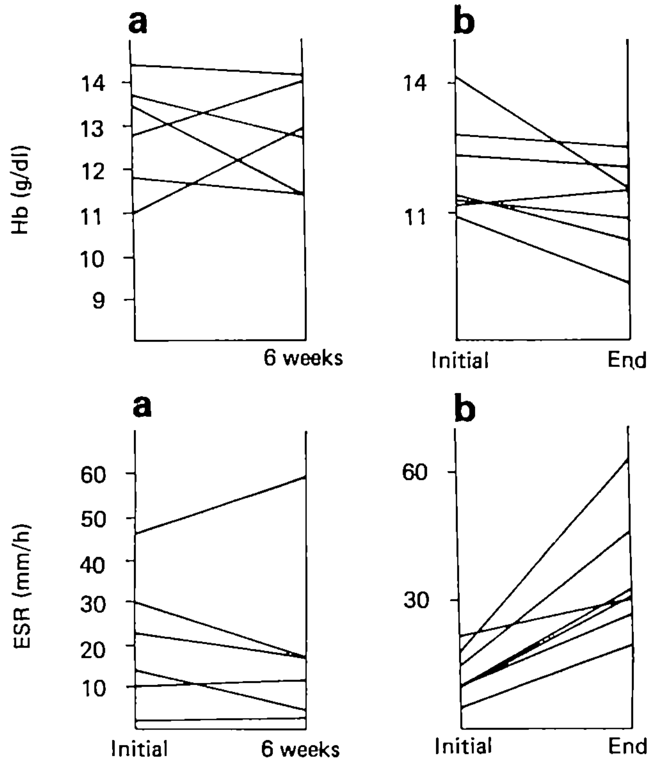

Figure 3 *Changes in haematological indices during cyclosporin treatment: comparison of* **a** *responders,* **b** *non-responders*

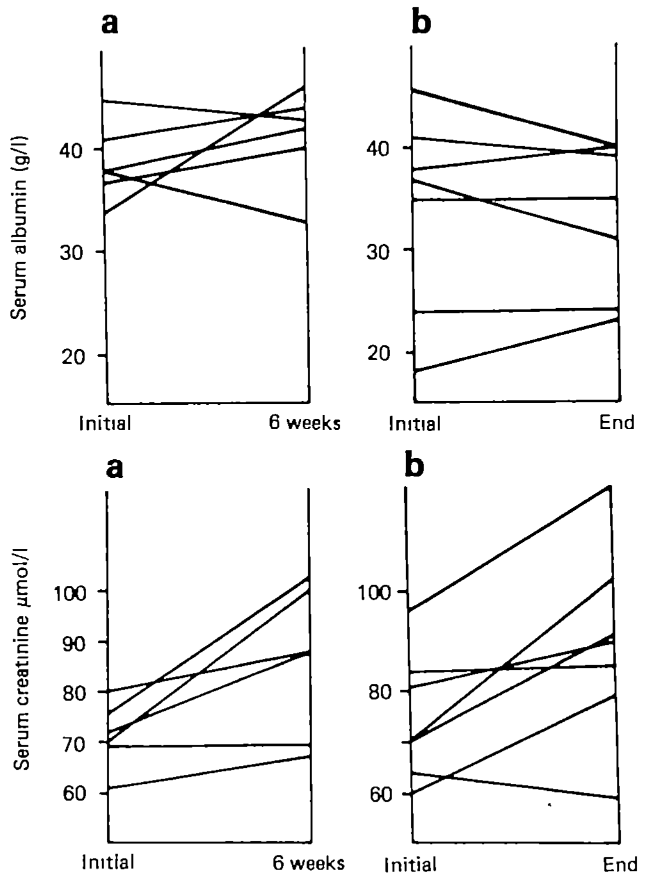

Figure 4 *Changes in biochemical indices during cyclosporin treatment: comparison of* **a** *responders,* **b** *non-responders*

cyclosporin A, but we have avoided this route because of occasional episodes of anaphylaxis that have been reported. The side-effects of treatment with cyclosporin A are generally in line with those reported in organ transplantation. The commonest side-effect is that of nephrotoxicity[8] and, although it has generally been regarded as dose dependent and reversible, there have been cases of end-stage renal failure secondary to long-term therapy[9]. In only one of the present cases was there a significant rise in serum creatinine during treatment with cyclosporin A, but it is interesting to note that the majority of patients had a slight rise in serum creatinine after treatment started. It may be that these changes are related to altered nutrition of the patients, but the clinical course of the patients would suggest that it is more likely to be related to a mild degree of nephrotoxicity. The occurrence of hepatotoxicity is also well documented, and occurs in 11–48 per cent of patients[10–12]. The single case in this series is most likely to be related to cyclosporin A. It is not clear why the response rate in the present study is so much lower than that reported by Allison and Pounder. Both studies involved patients with disease of the large and small bowel, and have cases of roughly equivalent severity. In the National Cooperative Crohn's Disease Study[13], the placebo response rate was 40 per cent, while the response to steroids was 65 per cent at 6 weeks Reference to such historical controls may be misleading However, the high cost and adverse effects suggest that cyclosporin A is unlikely to replace steroids as the major form of therapy for Crohn's disease. It may have an important role as second-line therapy, and its use in combination with steroids remains to be determined

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A protocol for the safe treatment of acute lower limb ischaemia with intra-arterial streptokinase and surgery

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Over a 5-year period 70 patients, presenting with subacute ischaemia of the lower limb (more than 12 h), were treated with low-dose intra-arterial streptokinase. There were 72 infusions and effective lysis was achieved in 52 (72 per cent), with an average infusion time of 25 h. A total of 23 (32 per cent) also underwent percutaneous transluminal angioplasty when lysis showed an underlying stenosis, and a further 19 (26 per cent) required surgery to remove persistent stenosis, organized thrombus or atheromatous debris. Significant bleeding occurred in 4 patients (6 per cent) and 13 (18 per cent) underwent amputation. There were five deaths (7 per cent), one of which was directly related to the infusion, while three were due to myocardial infarction. All of the major complications occurred in the early part of the study and both the selection of patients and the technique of infusion were modified to improve safety. Complementary treatment by percutaneous transluminal angioplasty and surgery was used more frequently in the later part of the study. The technique is not recommended for the white leg of acute ischaemia (<12 h), or for lysis of clot in a retroperitoneal Dacron® graft, but may be uniquely valuable to demonstrate the cause of subacute ischaemia.

Keywords: Arterial occlusion, arterial thrombosis, arterial thrombolysis, arterial embolectomy

Acute ischaemia of the lower limbs is associated with a high morbidity and mortality in all published series[1–4]. The results of surgery were significantly improved by the introduction of catheter embolectomy in 1963 but, even with modern surgical management, up to one-third of patients face amputation and mortality rates in excess of 15 per cent are common

In 1971 Chesterman *et al.* reported the use of low-dose intra-arterial streptokinase therapy to clear vessel thrombosis following vascular injury[5], and in 1972 Dotter *et al.* described the technique in seven patients with arterial occlusions[6]. Since then, the use of catheter embolectomy has become universally accepted but intra-arterial streptokinase with its unique advantages has not been widely used, probably because of technical difficulties in placing the infusion catheter and reports of dramatic haemorrhage.

In 1982 a protocol for the controlled use of intra-arterial streptokinase in acute lower limb ischaemia was agreed between a vascular surgeon (A.E.B.G.) and radiologist (W.J.W.) and was subsequently modified to improve safety and efficacy[7]. This report presents the results of treatment in 70 patients (72 infusions), and factors in patient selection and technical management which have been found crucial to a successful and safe outcome.

Patients and methods

All patients presenting acutely with lower limb ischaemia over a 5-year period were jointly assessed by a vascular surgeon and a radiologist for possible streptokinase therapy. Twenty-three patients seen within the first few hours of an occlusion and showing a 'white leg', characteristic of initial arterial spasm, were treated by conventional catheter embolectomy. Neither these patients nor the 56 patients with subacute ischaemia treated with heparin alone, nor those with calf muscle necrosis requiring primary amputation, are included here Patients were considered for streptokinase therapy regardless of the presumed duration of occlusion. They underwent a full diagnostic arteriogram from the contralateral groin. In only three cases was an ipsilateral approach used. If the occlusion appeared suitable for infusion, a straight 5 FG catheter with two side holes, approximately 1 cm from the tip, was embedded 1–2 cm into the obstructing thrombus, again from the contralateral groin Streptokinase (Kabikinase®, KabiVitrum) was infused in a dose of 5000–6000 units/h for up to 54 h. A dose of 7000–10 000 units was given in six cases early in the series. The patient was nursed flat in the intensive care unit. A single-shot arteriogram was carried out 6–14 h later, using non-ionic contrast media. If there was a clinical deterioration over 6 h, urgent surgery was undertaken. If there was a rapid improvement, the catheter was advanced. If there was no improvement, assessment was delayed for a maximum of 12–14 h. If a stenosis or an occlusion of <6 cm was found, immediate balloon angioplasty was carried out, usually by an antegrade approach. After angioplasty of the stenotic segment, streptokinase was directly infused through the angioplasty catheter and saline was given to maintain patency of the contralateral catheter. Restoration of pedal pulses did not preclude further percutaneous transluminal angioplasty or surgery if angiographic evidence of residual stenosis, clot or debris was present

If no lysis was evident after 12 h, surgical exploration and thrombectomy were undertaken The contralateral catheter was not disturbed during exploration but was positioned proximal to the arteriotomy so that intra-operative and postoperative arteriograms could be obtained

At the end of treatment, a bolus of 1000 units of heparin was given through the infusion catheter and the streptokinase discontinued. An infusion of 800 units/h of heparin was given, also through the catheter, and intravenous heparin cover was continued when arterial catheters were removed 4–5 h later After removal, firm digital pressure was applied to the puncture site, sufficient to stop bleeding but not to occlude the vessel completely

Where there was effective lysis but distal embolization occurred as the clot fragmented the infusion was continued to promote further lysis of the fragments. Where effective lysis of propagation clot revealed persistent filling defects, despite a further 6 h infusion, surgical exploration was undertaken. These defects were found to be due to organized mature thrombus or atheromatous debris.

Results

Most patients had extensive thromboses: only 11 had segmental occlusions, and 7 of these were longer than 9 cm. The sites of occlusion are shown in *Table 1*. Using this protocol, 70 patients underwent 72 infusions (2 patients had 2 infusions on separate occasions for different lesions). The results are given in *Tables 2* and *3*. Forty-five of these cases presented with spontaneous arterial thrombosis and two following percutaneous transluminal angioplasty. There were 11 patients with systemic emboli and 7 treated for thrombosis of femoropopliteal grafts. Five patients with a thrombosis of a popliteal aneurysm and two who had thrombosis in aortobifemoral grafts were also treated.

Effective lysis was deemed to have occurred when between 70 and 100 per cent of the obstructing clot had disappeared and this was achieved in 52 patients. The average lysis time was 25 h and this did not change between the first 26 patients reported in 1985[7] and the second part of the series. Angioplasty and surgery were, however, much more frequently employed in the later part of our experience, 3 angioplasties being used in the treatment of the first 27 cases, but 20 in the remaining 45. Of the first 26 patients, only 5 were operated on, but 14 of the next 44 patients received surgery. Thirteen patients (18 per cent) underwent amputation. At least three of these were already committed to amputation but, at the time, an attempt at thrombolysis seemed justified, hoping to lower the level of the amputation.

One patient died as a result of a direct complication of treatment when haemorrhagic collapse precipitated aspiration of gastric content and subsequent death. There were four other deaths, none of which was directly attributable to the technique, resulting in a mortality of 7 per cent. One patient developed haemorrhage into the popliteal fossa and required blood transfusion. Two patients suffered distal embolism, one developed prolonged ileus, one an allergic reaction, and one a minor pericatheter thrombosis. All of these complications occurred in the first 27 infusions and have been previously reported in detail[7]. We would now regard them as preventable. Surgical treatment after streptokinase is detailed in *Table 4* and the final protocol is shown in *Figure 1*.

Discussion

There has been widespread recent controversy about the role of low-dose intra-arterial streptokinase in the treatment of acute arterial occlusion. Anecdotal reports of success[8,9] have been countered by allegations that the technique is both ineffective and risky[10–12]. While there is definite evidence that thrombolysis is dangerous in some situations, for example the lysis of clot in a retroperitoneally placed Dacron® (E.I. Dupont de Nemour Incorporated) graft[13], much of the controversy has arisen because of the wide variation in patient selection and infusion techniques. Our experience has shown that the use of streptokinase is justified when correct selection and technique are used.

The need to use intra-arterial streptokinase

Even the most stringent critics of the technique admit that there are three situations in which it may be justified[14]. These are acutely thrombosed popliteal aneurysms with tibial artery thrombosis, thrombosis of an autogenous vein graft, and embolization of a cardiac thrombus following acute myocardial infarction. The natural history of the ischaemic limb and the limited success of conventional surgery strongly support the need for better diagnosis and treatment, and streptokinase may help in both.

Acute occlusion initially produces arterial spasm, clinically obvious as a cool white leg[1]. This situation is an indication for urgent thrombectomy. After 6–12 h, arterial spasm gives way to dilatation and the vessels fill with stagnant blood bounded by a thrombogenic intima. This late phenomenon is seen clinically as a cold blue leg and is a common presentation, the limb often being ischaemic but just viable. Such patients can no longer anticipate good results from conventional catheter thrombectomy and include those with thrombosis of

Table 1 *Site of occlusion*

Site	*n*
Superficial femoral artery	29
Popliteal	20
Femoropopliteal graft	7
Iliac	6
Common femoral	4
Aortobifemoral graft	2
Calf vessels	2
Distal aorta	1
Brachial	1
Total	72

Table 2 *Results of thrombolysis, angioplasty and surgery: early and total experience*

Result	Cases 1–27	All cases
Effective lysis (70–100%)	16 (59)	52 (72)
Average lysis time (h)	25	25
Streptokinase and angioplasty	3 (11)	23 (32)
Streptokinase and surgery ± angioplasty	5 (18)	19 (26)
Significant bleeding	4 (15)	4 (6)
Amputations	8 (30)	13 (18)
Deaths	2 (7)	5 (7)

Patients with lower limb ischaemia, 70, number of infusions (cases), 72, percentages in parentheses

Table 4 *Surgery after streptokinase infusion*

Procedure	*n*
Amputation	13
Endarterectomy/surgical angioplasty	10
Bypass graft	5
Removal of clot or debris	2
Sympathectomy	1
Suture of iliac vein laceration	1
Total	32

Table 3 *Results of thrombolysis: types of occlusion*

Type of occlusion	No. of infusions	Effective lysis	Significant bleeding	Amputation
Thrombosis of artery	45	29	2	7
Embolus	11	8	0	0
Thrombosis of femoropopliteal graft	7	7	1	4
Thrombosis of popliteal aneurysm	5	5	0	0
Thrombosis of aortofemoral graft	2	1	1	2
Thrombosis after angioplasty	2	2	0	0
Total	72	52	4	13

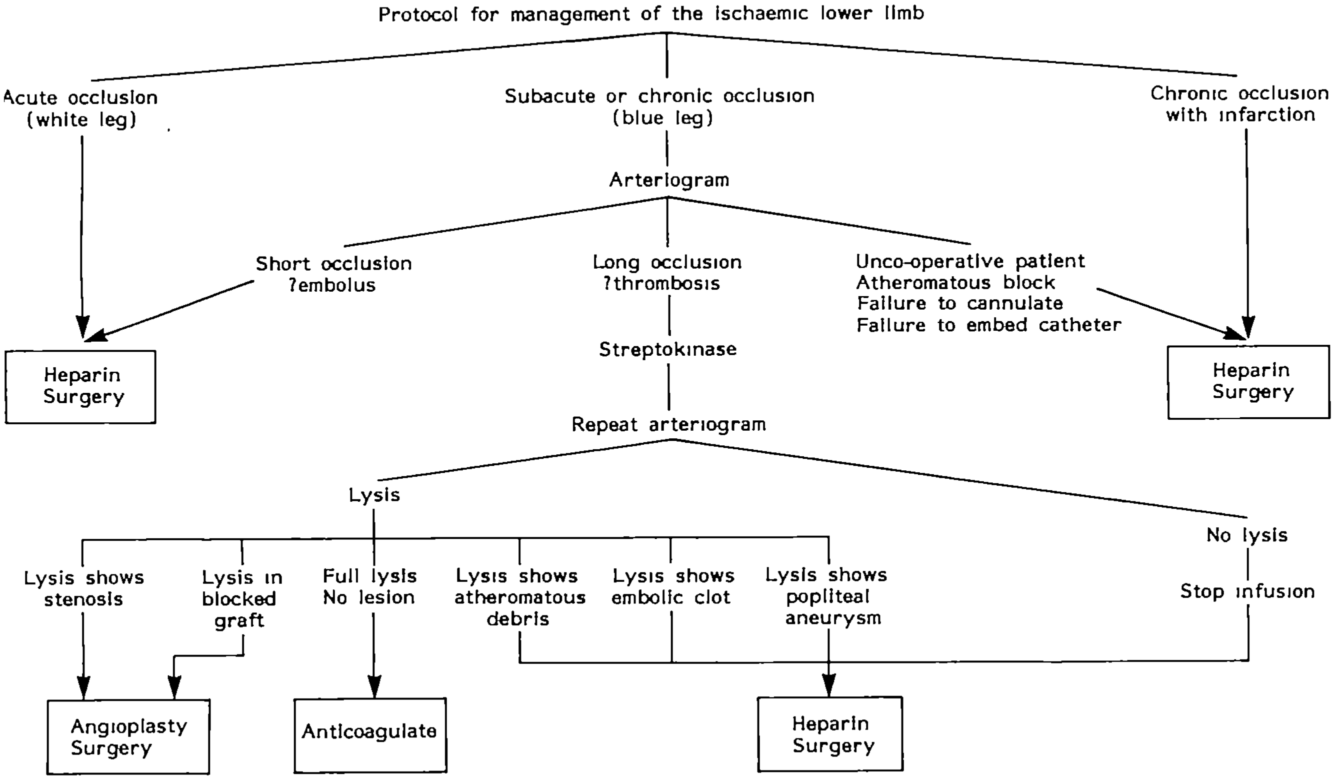

Figure 1 *Protocol for the management of the ischaemic lower limb*

atheromatous arteries or popliteal aneurysms. Clearance by physical methods is rarely associated with a satisfactory outcome. Critical evaluation of catheter embolectomy, even for relatively acute emboli, shows no cause for complacency. In a review of 90 consecutive patients with 121 arterial emboli, Kendrick *et al.* in 1981 noted a mortality rate of 40 per cent and an amputation rate of 27 per cent when the procedure was performed 7–12 h after the onset of symptoms[2]. For patients with a later presentation, the results of thrombectomy were even worse with an amputation rate of 52 per cent and a mortality rate of 48 per cent, 13–48 h after the onset of symptoms. As Earnshaw *et al.* have shown[9], even with modern surgical treatment, patients with acute peripheral arterial ischaemia have only a 70 per cent chance of surviving to leave hospital with an intact limb. Improvement in these results should be possible if propagation clot can be removed and the cause of the occlusion shown and treated. Streptokinase offers that chance.

The safe management of thrombolysis

Selection of patients. It is important to exclude those patients with an early presentation of classic embolic occlusion who are best treated by urgent thrombectomy, and those with muscle necrosis who require primary amputation. There remains a large group of patients for whom conventional thrombectomy would be too late and, in many of these patients the cause and duration of the occlusion is unknown The limb remains just viable and, for these patients, there are three options: (1) attempted thrombectomy with the prospect of a poor result and high mortality; (2) intra-arterial thrombolysis, if it is technically feasible and safe; (3) the use of high-dose intravenous heparin, which has been shown by Blaisdell *et al.* to reduce mortality without increasing limb loss when compared with thrombectomy[1]. In deciding between these options, it is essential to assess both the site of the occlusion and the state of the patient. A full diagnostic arteriogram, carried out by puncture of the contralateral femoral artery, is not merely 'useful'[3], but essential in that decision process.

If a discrete short segment occlusion is revealed with little or no propagation clot, suggesting a surgically removable thrombus or embolus, thrombectomy is appropriate. In most patients with a subacute presentation, extensive propagation clot is likely and, for the treatment of this, streptokinase is suitable. The treatment requires patience and those patients who are unwilling or unable to co-operate must be excluded at this stage.

The infusion catheter. The radiologist must be able to wedge the infusion catheter into the obstruction from the contralateral groin. This requires expertise but significantly reduces both bleeding and instability. In the series reported by Earnshaw *et al.*[9], of 40 patients in whom infusion was attempted, the catheter could not be satisfactorily positioned in 8 and it broke or fell out in 4; and in the series reported by Pernes *et al.*[11], in which the ipsilateral femoral approach was used more than twice as frequently as the contralateral approach, a high incidence of bleeding and catheter-related thrombotic problems was reported. In the series reported here, a contralateral approach was used in all but three patients. When an ipsilateral antegrade approach is made, a high puncture is required, several centimetres above the inguinal ligament. At this point the vessel lies deeply and a side wall puncture may be unavoidable There is also a tendency for the guidewire to enter the profunda femoris artery and multiple punctures increase bleeding complications. After withdrawal of the catheter, compression is less precise owing to the depth of the vessel in its supra-inguinal course.

As infusion may be given over 24–48 h, the catheter should be as small as possible to permit strong pericatheter blood flow. This reduces the risk of spasm and pericatheter thrombosis which is reported in some series to be up to 25 per cent[11]. Good flow avoids the need for concurrent heparin therapy which significantly increases the risk of bleeding. In this series, pericatheter thrombosis occurred in only one case. To encourage pericatheter flow, it is wise to dilate proximal stenoses before or at an early stage in the infusion.

Conduct of the infusion. A satisfactory wedging of the infusion catheter 2 cm into the clot is mandatory if the desired high local concentration of streptokinase is to be achieved and the infusion should not be given if there is rapid dilution by flow into adjacent collaterals.

Techniques of infusion vary from the continuous infusion, reported here, to the use of discrete bolus injections of 2500 units every 5 min as first described by Hess *et al.* in 1982[15] and recently reported by Lammer *et al* in 1985[16]. While the latter technique is relatively speedy (1–7 h), the radiologist's time commitment is very high when compared with our protocol where he is needed only for the positioning of the catheter and to review progress every 12–14 h. When the 12 h film shows lysis, treatment is continued and any angioplasty or repositioning of the catheter is carried out. If there is no lysis at 12 h, or no further lysis after a 12 h interval, the infusion should be stopped. Angioplasty or reconstruction, if possible, should then be carried out as soon as practicable as untreated stenosis or filling defects carry at least a 15 per cent risk of rethrombosis at the same site. After angioplasty, further streptokinase may be required to treat residual distal clot and it can conveniently be given through the angioplasty catheter.

To conform to a strict protocol, streptokinase alone has been used. The recent report of van Breda *et al.* suggests that urokinase may become the drug of choice because patients are not resistant or allergic to it[17], but it seems unlikely that any lytic agent is clearly superior in reducing the incidence of unwanted bleeding because that side-effect is a feature of potency. Complications are best avoided by attention to the details of administration rather than by the minor differences in the properties of the agent. The only patient in this series to show an allergic reaction was satisfactorily controlled with hydrocortisone, although the infusion had to be stopped.

In the first 27 cases treated, a number of parameters were measured to assess the bleeding and clotting profiles[18,19] during infusion. These tests included fibrin titre, thrombin time and fibrin degradation product levels, but no change was found to be of practical help in predicting haemorrhagic complications. There was clinical evidence of systemic fibrinolysis in all of those patients in whom the infusion lasted for more than 24 h, even at the low dosages used. This tendency increased in severity with the length of the infusion and, as occlusions not responding to thrombolytic therapy within 12 h were unlikely to do so in 24 h, the policy has been for frequent assessment and early withdrawal of an ineffective infusion as the most important safeguards against bleeding.

Is treatment by streptokinase sufficient?

Published reports show widespread variation in the frequency of other measures to complete the salvage of the ischaemic limb. Angioplasty and surgery are considered as essential complementary techniques, but this is not universally accepted[8]. The role of streptokinase in the diagnosis of the cause of the ischaemia is profitable only if the cause can be treated The ability to dissolve propagation clot and show the embolus, atheromatous debris, stenosis or aneurysm should be followed by immediate angioplasty or surgery to secure more permanent benefit. As vascular surgeons have learned, it is important that an apparently good clinical result should not be accepted without angiographic proof of a satisfactory inflow and outflow to the affected segment; even the return of pulses to the foot does not guarantee stable perfusion if there is residual thrombus or stenosis, and the dissolution of thrombus which only partially obstructs flow is more difficult than where a complete occlusion allows pooling of the active drug Incomplete obstruction is best treated by surgery; but as experience was gained in this series, both surgery and angioplasty were more frequently employed. In our first 27 cases, only 3 were treated with angioplasty and 5 by surgical thrombectomy and reconstruction, but in the nex 45, angioplasty was employed in 20 and surgery in 14.

This study demonstrates that, with strict attention to detail thrombolysis is a valuable complementary technique to surgery and percutaneous transluminal angioplasty in the treatment o subacute arterial occlusion. Increasing experience has reduced complications and improved the likelihood of accurate diagnosis and appropriate treatment of the threatened limb.

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Amputation for peripheral vascular disease: the case for level selection

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One hundred major lower limb amputations were performed for end stage peripheral vascular disease over a 15-month period. Selection of amputation level was made on the basis of laboratory criteria using skin blood flow and infrared thermography data. Eighty-one amputations were performed at the below-knee level with six failures. This resulted in a final below-knee:above-knee amputation ratio of 3:1. It is clear that there are still many centres in the UK where above-knee amputation is the accepted operation, despite the inherent drawbacks to this procedure. We recommend that more attention is given to achieving higher below-knee amputation rates to improve the chances of amputee mobility and therefore quality of life.

Keywords: Amputation, skin blood flow, thermography

Advances in vascular surgical techniques and the increase in the number of vascular surgical reconstructions have not reduced the number of major lower limb amputations over the past decade[1]. Consequently, amputation at the above- and below-knee level continues to be a necessary part of the management of patients with end stage peripheral vascular disease. While the decision to amputate is entirely a clinical matter requiring experience and judgement, the selection of the optimum level of amputation, which depends upon the healing potential of a specific skin flap, often defeats even the most trained observer. To ensure primary wound healing, one can opt for an above-knee amputation in preference to a below-knee procedure and indeed many prefer the near certainty of outcome—as reflected by the national statistics[1]. However, the penalty for this conservatism can be measured in terms of both patient mortality and morbidity in addition to a less satisfactory cosmetic and rehabilitation outcome[2].

In a retrospective review of amputation results obtained over a 5-year period, McCollum *et al* suggested that it should be possible to attain a below-knee:above-knee amputation ratio of 3:1 in conjunction with a healing rate of 90 per cent or better[3]. We conducted a prospective study to examine the role of skin viability assessment using radioisotope clearance, infrared thermography, and segmental systolic pressure measurements. The objective was to improve the ratio of below-knee:above-knee amputations whilst maintaining a reasonable wound healing rate.

Patients and methods

Over a 15-month period, 100 consecutive patients had limb viability studies carried out in the vascular laboratory within 24 h of major lower limb amputation surgery. All had end stage peripheral vascular disease which was either unsuitable for vascular reconstruction (59) or which had resulted from a failed bypass procedure (41). Laboratory criteria for deciding upon the optimum level of amputation was based on circumferential skin blood flow measurements, previously described[4]. Clearance studies were carried out at fixed anatomical points (two anteriorly, 10 cm distal to the tibial tuberosity and one posteriorly, 15 cm distal to the tuberosity. A mean (of three) skin blood flow of 2·5 ml 100 g^{-1} min^{-1} was taken as the lowest critical level below which healing was unlikely to occur. However, if an individual skin blood flow was <2·0 ml 100 g^{-1} min^{-1} the level of viable tissue was outlined by the circumferential thermographic perfusion image which was calibrated by spot measurements[5] A modified below-knee flap can be outlined in this way[6] and was implemented in six patients. The laboratory recommendation of the optimum level was not always accepted: in nine patients amputation was performed at the above-knee level on clinical grounds alone (either because of knee flexion contracture or because of stroke) These patients have been included in the results as they represent a problem familiar to all amputating surgeons

All amputations were performed by the orthopaedic team using standard techniques. Below-knee amputation stumps were encased in plaster of Paris and early mobilization (using a pneumatic walking aid) and limb fitting was instituted after transfer to the limb fitting centre—generally within 1 week of operation. Wounds were inspected 1 week after the operation. Patients were followed up postoperatively and healing was deemed to have occurred if the wound was sound 1 month after operation—thus enabling final prosthetic fitting to be carried out.

Results were analysed using the Mann–Whitney *U* (two-tail) test for non-parametric data.

Results

There were 19 above-knee amputations and 81 below-knee amputations. Only 10 of the 19 above-knee amputations were recommended on laboratory criteria, the remainder being performed because of co-existent medical problems (stroke and flexion contractures). The mean patient age was 76 years for above-knee amputees and 72 years for below-knee amputees (P=n.s.). In all, 41 patients had previous reconstructive surgery performed within Tayside region which ultimately failed, but this did not influence the outcome of healing.

All 19 above-knee amputees healed at this level although 1 required a further revision. There were six failures in the below-knee group while a further five required a wedge resection before achieving healing and nine stumps had delayed primary healing. All skewed flaps healed at the below-knee level.

Mean skin blood flow measurements for diabetics and non-diabetics are shown in *Table 1*. Mean systolic pressure measurements are shown in *Table 2*. Mean skin blood flow for below-knee amputation failures was 7·3 × 3·1 ml 100 g^{-1} min^{-1}. There were 45 diabetics (45 per cent) including those patients

Table 1 *Mean below-knee skin blood flow in above- and below-knee amputation groups*

	Below-knee skin blood flow (ml 100 g^{-1} min^{-1})			
	Diabetics	*n*	Non-diabetics	*n*
Above-knee				
Recommended (*n* = 10)	1·0±1·3	3	1·3±0·9	7
Not recommended (*n* = 9)	8·5±7·6	2	6·5±3·9	7
Below-knee (*n* = 81)	9·6±5·2*	40	8·4±3·3*	41

The values are mean±s.d. * P<0·001: Mann–Whitney *U* test (two-tail), below-knee *versus* above-knee (recommended)

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Table 2 *Segmental systolic pressure measurements in above- and below-knee amputation patients*

	Systolic pressure (mmHg)			
	Thigh	Calf	Ankle	Ankle/arm
Above-knee				
Recommended ($n=10$)	68±22	17±15	15±16	0·11±0·14
Not recommended ($n=9$)	102±47	57±26	49±32	0·31±0·28
Below-knee				
Diabetic ($n=40$)	130±68*	101±56*	81±55*	0·52±0·33*
Non-diabetic ($n=41$)	106±48*	58±27*	45±22*	0·29±0·14*

The values are mean ± s.d. * $P<0{\cdot}001$: Mann–Whitney *U* test (two-tail), below-knee *versus* above-knee (recommended)

who had impaired glucose tolerance (fasting blood sugar $>5{\cdot}7<7{\cdot}0$ mmol l^{-1}). There were an equal number of diabetics and non-diabetics in the below-knee group (*Table 1*) but only 5 of 19 above-knee amputees were diabetic. There was no significant difference in healing rates between diabetics and non-diabetics.

Discussion

The advantages of the below-knee amputation over the above-knee procedure are well documented and described elsewhere[2,7] but below-knee amputation effectively results in a greatly improved chance of mobility in conjunction with an improved morbidity and reduction in patient cost. The mobility rate for below-knee amputations in this unit is about 90 per cent[8]. Despite these obvious benefits, the relative number of above-knee to below-knee amputations in England and Wales has not decreased since the early 1970s, when the long posterior skin flap, popularized by Romano and Burgess[9], became widely accepted as the technique of choice for below-knee amputations. In fact, it is obvious that there are still more above- than below-knee amputations being performed in many areas of the UK[1]. A preference for the above-knee amputation cannot be justified on the grounds that the below-knee amputation fails to heal because it is evident from other studies that this is simply not true[10,11]. Not every surgeon has access to the (relatively) sophisticated assessment techniques described here, but a thigh systolic pressure measurement alone might ensure a much greater successful below-knee amputation rate if a value of 50 mmHg was used as the lower critical limit[12,13]. Extrapolating data from the Hospital Inpatient Enquiry[1], it is conceivable that up to 1000 above-knee amputations per year could have been performed at the below-knee level.

The problem of amputation level selection is not new and a wide variety of different methods have been applied to the prediction of the most distal level of healing attainable. This has been prompted by the poor correlation of wound healing with clinical signs and symptoms of tissue viability[14]. Amongst the more popular methodologies currently in use are Doppler pressure measurements[15], transcutaneous oxygen measurements[16], fluorescein angiography[17], infrared thermography[18] and radioisotope clearance[10].

Barnes *et al.*[15] suggested that an ankle pressure of >70 mmHg was consistent with healing in a below-knee amputation but this level does not even fit the criteria for critical ischaemia[19]. If this ankle pressure criterion was applied to the present study, then 43 patients would have had an unnecessary above-knee amputation. Dean *et al.*[12] and Holstein and Lassen[13] showed that healing could be expected where the thigh pressure was >50 mmHg, a finding confirmed by our data, although five patients in our study achieved healing with a pressure value below this. This may reflect patency of the profunda femoris artery which is likely to be important for healing in the presence of invariable superficial femoral artery occlusion.

The validity of the radioisotope clearance technique has been demonstrated by Malone *et al.*[10] who described the selection of amputation level using xenon-133. We have preferred [^{125}I] iodoantipyrine which has a linear washout and is unaffected by lipid affinity[20]. The relationship between skin blood flow value and thermography is good in the ischaemic lower leg[21], and it is significant that there was a prediction disagreement in only 1 of the 100 cases presented here. In this patient, skin blood flow suggested healing but thermography did not and the resulting below-knee amputation actually failed to heal.

While the methods used here have been developed to reduce below-knee amputation failures to a minimum, there were six below-knee failures. The causes of these failures included two severe stump infections and two stumps with ischaemia. A further two failures resulted from poor operative technique, where excess skin tension was applied to compensate for skin flaps which were too short.

The present results have been achieved by a regional and team approach to the management of the amputation patient, beginning with the initial assessment and continuing through operation into the immediate and later postoperative phases. While this system may encourage a more aggressive approach to the rehabilitation of the amputee[8], the absence of such a system should not preclude the majority of amputations being performed at the below-knee level. There is sufficient evidence to suggest that the centralization of amputation services with rehabilitation facilities will greatly improve patient morbidity[22], but it is probably economically unrealistic to expect this throughout the UK.

The number of major amputations being performed continues to increase[23], and the relatively high number of above-knee amputations, currently being performed, must be condemned. We feel that the adoption of adequate pre-amputation level assessment would result in a marked improvement in below-knee amputation rates, with a consequent increase in patient mobility and independence.

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Method for securing suction drains

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The use of sealed envelope-type suction drains is widespread but controversial[1]. A common method for securing the drain to skin is to use a 'sandal strap' style of ties for a short distance along the tubing. Although increased friction can be obtained with braided suture material, the knots may slip resulting in drain displacement.

The method described here involves passing the drain suture through skin, a terminal drain hole and back through skin again, where even a loose knot may be thrown (*Figure 1*). Furthermore, monofilament material may be used to reduce tissue reaction. This technique provides complete comfort to the patient, the drain cannot slip through any knots, but the nursing staff must be shown where the anchorage suture lies before removal.

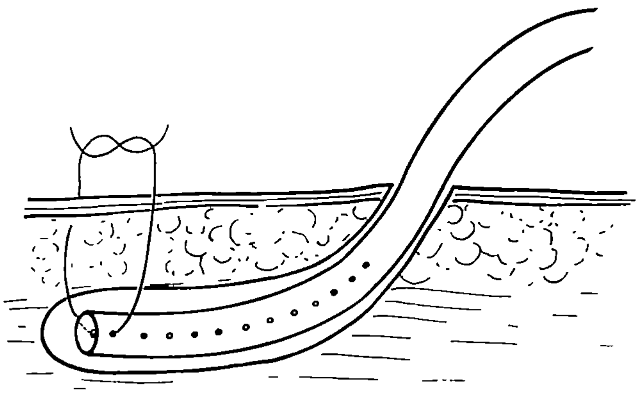

Figure 1 *Suction drain secured* in situ

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Local thrombolytic therapy of acute peripheral arterial ischaemia with tissue plasminogen activator: a dose-ranging study

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Low-dose streptokinase has been established as an alternative to surgery in selected patients with acute peripheral arterial ischaemia. Tissue plasminogen activator (t-PA) is responsible for normal plasma fibrinolytic activity and has recently become available for clinical use owing to recombinant DNA technology. It has the theoretical advantage of fibrin specificity, which may result in enhanced thrombolytic effects with greater safety. Twenty-three patients with recent lower limb arterial occlusions received t-PA over a tenfold range of concentrations and five patients received low-dose streptokinase. One month after treatment with t-PA or streptokinase 19 (68 per cent) patients had limb salvage, five (18 per cent) had required amputations and four (14 per cent) had died. Systemic fibrinolytic effects were variable but basically dose related. Haemorrhage occurred most frequently at the highest t-PA concentration and was major in four (17 per cent) cases, including a fatal stroke. Plasma fibrinogen concentration fell below $1{\cdot}2\ g\ l^{-1}$ in five (22 per cent) patients who received t-PA and was found to be a significant risk factor for haemorrhage. t-PA was an effective thrombolytic agent at all concentrations studied. The dose currently used in clinical studies at this institution is $0{\cdot}5\ mg\ h^{-1}$.

Keywords: Arterial thrombo-embolism, fibrinolysis, tissue plasminogen activator, streptokinase

Since Dotter *et al.* described low-dose intra-arterial streptokinase perfusion for peripheral arterial occlusions[1] the technique has become widely used as an alternative to surgery in selected patients[2–5]. However, reperfusion with streptokinase is relatively slow, often taking several days[3], so that peripheral blood flow in patients with severe ischaemia including neurosensory loss may not improve in time to prevent irreversible muscle necrosis. The formation of anti-streptococcal antibodies also precludes further use of the drug in the same patient for many months.

Tissue plasminogen activator (t-PA) is produced by normal vascular endothelium and is responsible for the maintenance of plasma fibrinolytic activity. It has recently become available in sufficient quantities for clinical use owing to recombinant DNA technology[6]. It has a theoretical advantage of an affinity for fibrin, which may make it an effective thrombolytic agent, yet safer than streptokinase or urokinase. In animal experiments t-PA has been shown to be an effective lytic agent in both venous and arterial thromboses without producing systemic fibrinolysis[7,8]. Animal dosimetry studies have established that concentrations 50 times higher than those in normal plasma were necessary for therapeutic clot lysis[9].

Most t-PA infusions have been given intravenously over short periods, and in early volunteer studies there was little effect on plasma fibrinogen if the duration of treatment was only 90 min[10]. Clinical studies of 90 min infusions have yielded satisfactory results in patients with acute myocardial infarction[11] and pulmonary embolism[12]. Infusion of t-PA in volunteers for longer than 90 min was found to produce a steady state of fibrinolytic activation with only limited fibrinogenolysis[13] t-PA has also been given by the intra-arterial route to patients with acute peripheral arterial occlusions, but the doses used ($0\ 05–0\ 1\ mg\ kg^{-1}\ h^{-1}$) produced significant fibrinogenolysis in up to 40 per cent[14]

Reports of t-PA infusions for longer than 90 min are rare and therefore in the present study patients with acute peripheral arterial occlusions have been treated over a tenfold range of doses to try to determine the concentration of t-PA which would produce therapeutic clot lysis with the minimum of fibrinogenolysis The clinical and haematological effects of t-PA at each dose were recorded and compared. A small group of patients who received low-dose intra-arterial streptokinase in the manner previously described by Dotter *et al*[1] were also included in the study for comparison.

Patients and methods

Patients

Twenty-eight patients were studied. All had limb-threatening peripheral arterial ischaemia of <1 month's duration. Thrombolysis was undertaken in these particular patients because they were regarded as being unlikely to have a good outcome from conventional surgical treatment because of advanced age, infirmity or the absence of good distal run-off on arteriography There were 23 men and 5 women with a median age of 65 5 years (42–83 years). Twenty-one (75 per cent) patients had suffered a recent arterial thrombosis, three (11 per cent) an arterial embolus, three (11 per cent) a graft thrombosis and one (4 per cent) a thrombosis after angioplasty. The median duration of ischaemic symptoms was 7·5 days (1–28 days) and the occlusion was situated in the iliac artery in 11 patients, the femoral artery in 15 patients and the popliteal artery in 2 patients The median length of the arterial occlusion at arteriography was 22 cm (from 5 cm to >30 cm). Fourteen (50 per cent) patients had occlusions >25 cm in length. One patient complained of severe claudication, but the remainder all had ischaemic pain at rest. Five (18 per cent) patients had severe ischaemia with a neurosensory loss at the start of treatment and four (14 per cent) had distal skin necrosis Median Doppler ankle brachial systolic pressure index before treatment was 0 3 (0–0 61) Seven (25 per cent) patients had no audible pedal blood flow using Doppler flowmetry. No patient was

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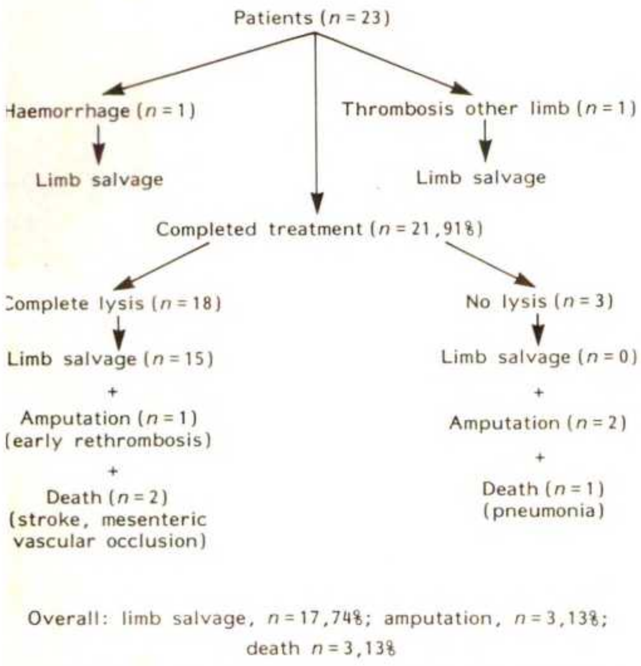

Figure 1 *Results of local tissue plasminogen activator perfusion in acute peripheral arterial ischaemia*

excluded from the study, although patients at high risk of bleeding complications or who had suffered a stroke in the previous 2 months would not have been suitable.

Intra-arterial thrombolytic therapy

All patients received local infusions of thrombolytic agents through a catheter situated at the level of the arterial occlusion. The arterial catheter was inserted at the time of diagnostic arteriography and the tip embedded in the arterial occlusion. The patients then returned to the surgical ward where the infusion of thrombolytic agent was commenced using a syringe pump. The following regimens were used: t-PA 2·5 mg h^{-1} (five patients); t-PA 1 mg h^{-1} (seven patients); t-PA 0·5 mg h^{-1} (six patients); t-PA 0·25 mg h^{-1} (five patients) and streptokinase 5000 units h^{-1} mixed with heparin 250 units h^{-1} (five patients).

Regular clinical examination was performed during treatment but the mainstay of assessment was arteriography performed via the arterial catheter 4 h after the start of the infusion and every 12 h thereafter, using portable X-ray equipment. The infusion continued until there was a clinical improvement, with vessel patency restored on arteriography. There was usually improvement with each successive arteriogram and, if none occurred between two 12-hourly films, the infusion was stopped. After recanalization, if a residual arterial stenosis was identified, the patient returned to the X-ray department where transluminal angioplasty was performed, usually before the catheter was removed. After successful lysis the patients received anticoagulant treatment with heparin and after 5 days were randomized either to long-term warfarin or antiplatelet therapy with aspirin 300 mg day^{-1} and dipyridamole 100 mg t.d.s., as part of a further study.

Haematological investigations and laboratory methods

The following fibrinolytic parameters were measured before, during and after treatment: thrombin clotting time, fibrinogen, fibrin degradation products, plasminogen and α_2-antiplasmin levels and euglobin lysis times.

Thrombin clotting time, plasminogen and α_2-antiplasmin levels were estimated on venous samples collected in 1/10 volume of 3·8 per cent trisodium citrate dihydrate, taken to the laboratory immediately after sampling. Platelet-poor plasma was obtained by centrifuging the citrated samples at 1500g for 10 min and either tested immediately or frozen at −50° for analysis later in batches. Plasminogen and α_2-antiplasmin assays were performed using a synthetic chromogenic substrate (S2251, KabiVitrum, Stockholm, Sweden)[15,16]. Fibrinogen was measured on venous samples transferred into 1/10 volume of 3·8 per cent trisodium citrate dihydrate with 10 per cent Trasylol (Bayer, UK Ltd., Newbury, UK) and stored as above. Samples were analysed later in barches by the method of von Clauss[17]. Euglobulin lysis times were estimated by the method of Buckell[18]. Fibrin degradation product assays were carried out on 2 ml venous samples using a latex agglutination kit (Baxter Health Care, Miami, USA).

Analysis

Arteriography was performed in the few days after thrombolysis was completed and the films compared with pretreatment arteriograms. Clinical examination of pulses and Doppler ankle systolic pressure measurements were contrasted with pretreatment values. Initial lysis was recorded as complete if there was angiographic recanalization with re-appearance of pulses distal to the occlusion. After 30 days, or at hospital discharge if this was sooner, a functional assessment was made: either limb salvage, amputation or death. The haematological results of each agent at the various doses were compared graphically. The clinical and haematological results were compared by χ^2 analysis.

Results

Clinical results

The median duration of infusion required to achieve reperfusion was 22 h in t-PA patients and 28 h in the streptokinase patients. In the t-PA group, two patients failed to complete a course of thrombolysis: in one the infusion was terminated because of bleeding and in the other an acute thrombosis of an aortobifemoral graft occurred in the opposite unaffected limb necessitating urgent surgery (*Figure 1*).

The infusions resulted in complete lysis with re-appearance of the pulses distal to the arterial occlusion in 18 (78 per cent) patients treated with t-PA and 2 (40 per cent) of the patients treated with streptokinase (*Figure 2*). In this group, the median ankle:brachial systolic pressure index improved from 0·35 (0–0·61) to 0·89 (0·5–1·08) (Mann–Whitney U test, $U = 6{\cdot}5$, $P < 0{\cdot}001$). Successful thrombolysis was not dose related and occurred at all concentrations of t-PA (*Table 1*). After lysis a residual arterial stenosis was identified and dilated by percutaneous angioplasty on 12 occasions. Limb salvage was achieved in only two of eight patients in whom thrombolysis was unsuccessful: one after graft thrombectomy and the other after surgical sympathectomy. One month later, limb salvage in the whole group had been achieved in 19 (68 per cent) patients, 5 (18 per cent) had required amputations and 4 (14 per cent) had died.

Only one of the four deaths was attributable to the haemorrhagic effects of thrombolysis. A 75-year-old man

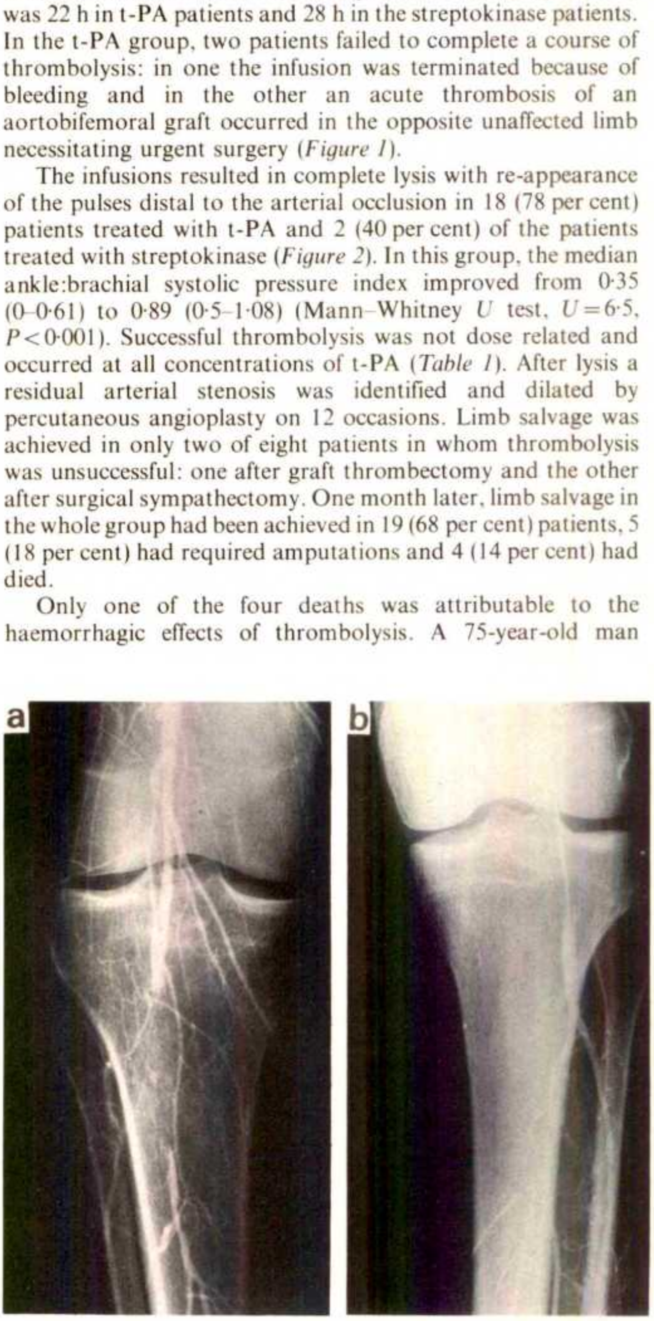

Figure 2 **a** *Popliteal artery occlusion (14 days old) causing rest pain in an elderly arteriopath with a history of previous vascular surgery (femoral crossover graft);* **b** *arteriogram taken during tissue plasminogen activator infusion before the catheter was removed demonstrating recanalization of the occluded arterial segment*

Table 1 *Results and complications of intra-arterial thrombolytic therapy with tissue plasminogen activator and low-dose streptokinase*

	Tissue plasminogen activator (mg h^{-1})					
Outcome/complications	0·25	0·5	1·0	2·5	Streptokinase (5000 units h^{-1})	Total
Total	5	6	7	5	5	28
Complete lysis	4	4	5	5	2	20 (71)
Limb salvage	4	4	5	4	2	19 (68)
Amputation	1	1	1	0	2	5 (18)
Death	0	1	1	1	1	4 (14)
Major haemorrhage	0	1	0	3	0	4 (14)
Minor haemorrhage	1	1	1	0	1	4 (14)

*Percentages are given in parentheses

developed a dense hemiplegia 30 min after t-PA therapy at 2·5 mg h^{-1}. He subsequently died and post mortem revealed two areas of intracerebral haemorrhage. One of the other patients died from acute massive intestinal ischaemia 48 h after thrombolysis (on heparin) and another from bronchopneumonia after failed thrombolysis before amputation could be performed. The death after streptokinase therapy was due to the extension of a femoral thrombosis to involve the aorta, again while receiving heparin.

Haemorrhagic complications occurred in eight (29 per cent) patients, usually at the site of arterial catheter puncture. Major haemorrhage requiring blood transfusion and minor groin haematomata occurred on four occasions each. The patient who had thrombosis of the functioning limb of an aortobifemoral graft during t-PA infusion at 0·5 mg h^{-1} developed a severe bleeding diathesis during graft thrombectomy which required cryoprecipitate and tranexamic acid for control of the bleeding. Haemorrhage seemed to be related to the dose of t-PA, being most frequent at 2·5 mg h^{-1} which was the highest concentration infused. All but one of the major complications occurred with this dose (*Table 1*).

Other complications of treatment included pericatheter thrombosis (one case) and distal embolization of fragments of lysing thrombus with deterioration of the limb (two cases); all resolved with continued infusion. The patient with a severe bleeding diathesis developed acute renal tubular necrosis and required peritoneal dialysis.

The main factor influencing outcome was the severity of ischaemia on presentation. Only one of the five patients with neurosensory loss had the limb saved, compared with 18 of the 23 with ischaemic rest pain alone ($\chi^2 = 6·1$, $P = 0·01$). Similarly, five of the seven patients with no systolic ankle blood flow failed to achieve limb salvage, compared with four of the twenty-one patients in whom ankle blood flow was detectable ($\chi^2 = 6·4$, $P = 0·01$).

Haematological results

The systemic fibrinolytic effects of t-PA were very variable, although broadly they reflected the concentration of t-PA infused (*Figure 3*). Plasma fibrinogen fell below 1·2 g/l in five (22 per cent) t-PA patients and two (40 per cent) streptokinase patients. Six of the eight bleeding complications occurred when plasma fibrinogen was < 1·2 g/l and this represented a major risk factor for haemorrhage ($\chi^2 = 14·4$, $P = 0·0004$). There did not appear to be much difference between the fibrinogenolytic effects of t-PA and low-dose streptokinase.

Plasma fibrin degradation products were elevated in most of the t-PA patients, generally to greater concentrations than with low-dose streptokinase. This probably reflected the speed of thrombolysis with t-PA. Plasma fibrin degradation products > 320 mg/l occurred in 15 (65 per cent) of the t-PA patients compared with only one (20 per cent) streptokinase patient ($\chi^2 = 3·5$, $P = 0·06$).

The effects of both t-PA and streptokinase on the thrombin clotting time and euglobulin lysis time were similar, showing a marked early systemic effect which lasted throughout the

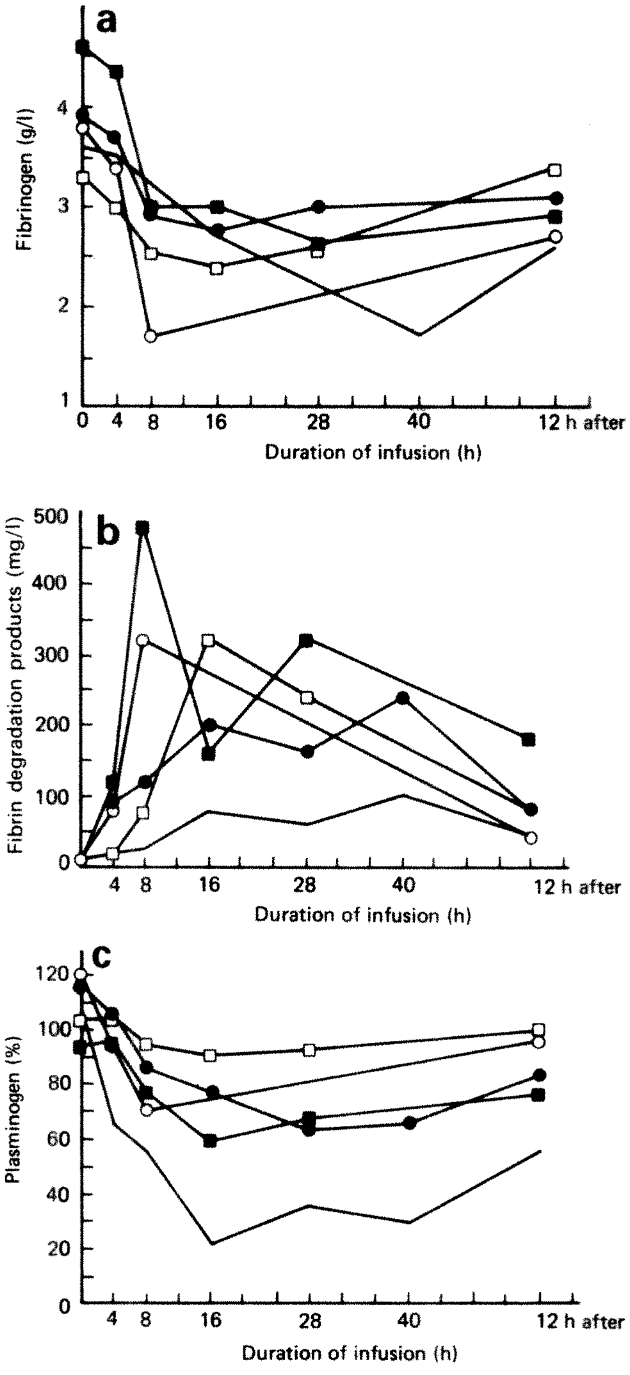

Figure 3 *Comparison of the systemic effects produced by intra-arterial tissue plasminogen activator (0·25–2·5 mg h^{-1}) and streptokinase (5000 units/h). Median values are shown for fibrinogen, fibrin degradation products, and plasminogen. Doses of tissue plasminogen activator:* ○, *2·5 mg h^{-1};* ●, *1·0 mg h^{-1};* ■, *0·5 mg h^{-1} and* □, *0·25 mg h^{-1}.* —, *Streptokinase*

infusions. There was, however, a relative sparing of plasminogen and, to a lesser extent, of α_2-antiplasmin with t-PA when compared with low-dose streptokinase.

Discussion

In many thrombotic conditions the concept of lysing fresh clots *in situ* is attractive and there is a possibility that t-PA may be a major advance over current first-generation thrombolytic agents such as streptokinase and urokinase. Although the clinical use of t-PA has become widespread in a short space of time, data on the optimum dose schedules remain sparse, especially for infusions of >90 min duration. Thrombolysis has been accepted as a primary method of treatment in arterial thrombotic conditions such as acute myocardial infarction and pulmonary embolism, and the possible benefits of t-PA are currently being evaluated in these conditions[11,12]. A randomized trial comparing intravenous t-PA and streptokinase in acute myocardial infarction has confirmed the superiority of t-PA with a reperfusion rate of 66 per cent; however, haemorrhagic complications were more common than expected[19].

In peripheral arterial ischaemia, surgeons have been reluctant to accept a role for thrombolytic therapy, although several large studies have documented excellent results in selected patients[1–5]. In an investigation at this institution low-dose intra-arterial streptokinase was shown to be an effective thrombolytic agent in patients not suitable for surgical treatment and a reperfusion rate of 69 per cent was achieved[20]. t-PA has been used previously in a study of 33 patients with peripheral arterial occlusions with an initial lysis rate of 97 per cent[14]. In the present study, weight-adjusted doses of t-PA were not used, to try to simplify the thrombolytic regimen. The concentrations infused ranged from about one-half to one-twentieth of those used in the reported series. The aim was to determine whether small doses of t-PA, equivalent to the low dose of streptokinase used in the Dotter regimen[1], could produce consistent lysis with a minimum of systemic effects and complications.

Lysis of the arterial occlusions occurred with all concentrations of t-PA infused and the median time taken for reperfusion (22 h) was a significant improvement on the previous times recorded at this institution (median 38 h)[20] and elsewhere (up to 120 h)[3] using low-dose streptokinase. In the study by Graor *et al.*, using a higher concentration of t-PA, it was never necessary to continue the infusion for more than 6 h[14]. The speed of lysis appeared to be dose related and, in future, higher concentrations might be used to achieve lysis in urgent situations where ischaemia was severe The alternative may be to exclude patients with severe ischaemia from thrombolysis as this study has confirmed that they are not good candidates for treatment.

Although the systemic fibrinolytic effects of t-PA were broadly dose related, there was considerable variation, the reason for which is not yet known. Complications occurred fairly frequently, although all but one of the major ones occurred at a t-PA concentration of $2{\cdot}5\ \mathrm{mg\ h^{-1}}$, the highest infusion rate. Although a systemic lytic state is not necessary for successful reperfusion, it has been shown to be a risk factor for haemorrhagic complications. A fibrinogen concentration of $1{\cdot}2\ \mathrm{g\ l^{-1}}$, measured by the technique of von Clauss[17], has been confirmed as a risk factor and the dose of t-PA should probably be reduced if this level is reached.

The fibrinogenolytic effects of t-PA and streptokinase were comparable. A plasma fibrinogen concentration $<1{\cdot}2\ \mathrm{g\ l^{-1}}$ occurred in 22 per cent of the t-PA patients, a number similar to that previously recorded using streptokinase[20]. Although there was a relative sparing of plasminogen and α_2-antiplasmin, an excess of fibrin degradation products was produced. Detailed examination of these products using monoclonal antibody techniques might provide information as to their source, but an excess of cross-linked fibrin degradation products has already been reported with t-PA therapy[21]. High concentrations of fibrin degradation products may increase the risk of bleeding due to their anticoagulant effect, although in this study excess fibrin degradation products did not correlate with the bleeding risk as well as a reduced plasma fibrinogen concentration.

In summary, t-PA has been found to be a useful thrombolytic agent over a wide range of concentrations in peripheral arterial ischaemia. Although the numbers in this study were small, complications occurred mostly at a concentration of $2{\cdot}5\ \mathrm{mg\ h^{-1}}$, and currently the dose of t-PA used in clinical situations at this institution is $0{\cdot}5\ \mathrm{mg\ h^{-1}}$. Although the exact role of intra-arterial thrombolysis is uncertain, it has been shown to be effective in acute peripheral arterial ischaemia. t-PA has been shown to be a suitable agent but, if it is going to replace first-generation drugs such as streptokinase and urokinase, randomized trials will be required to prove that its clinical effects are superior.

Acknowledgements

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Protection of the infected aortic stump: submucosal mesenteric pedicle grafts

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Infection of an aortic stump is a potentially devastating complication which requires removal of the graft. Two major surgical problems need to be overcome: (1) distal revascularization and (2) secure closure of the aortic stump. The solution to the former usually involves extra-anatomic bypass while the latter requires direct suturing of the aortic stump This is associated with a risk of aortic stump disruption, either in the perioperative period or much later. Persistent, but often subclinical, infection appears to be an important aetiological factor in aortic stump failure which may initially manifest as false aneurysm formation[1].

Traditionally, the omentum has been used to protect the aortic stump, but disruption remains a recognized problem. It is our contention that the primary role of the omentum is to 'wall off' areas of sepsis by tenuous adhesions. In the context of an aortic stump, such concentration of sepsis may in fact be detrimental. A more satisfactory solution would involve protection of the aortic stump by a highly vascular tissue surface with rich lymphatic drainage and the production of a dense fibrous reaction.

A mesenteric ileal pedicle graft which has these properties has been described for bridging inguinal lymphatic obstruction[2]. We have adapted this technique and used it in patients requiring excision of infected aortic grafts. Shah *et al.*[1] reported this application in 1983, but the procedure has not been widely adopted. The technique consists of the isolation and mobilization of a 3–4 cm segment of jejunum (*Figure 1a*). The small bowel is reconstituted by end-to-end anastomosis. The jejunal segment is opened longitudinally along the antemesenteric border and the mucosa is excised. The exposed submucosa is placed over the previously closed aortic stump and a series of absorbable tacking sutures inserted to maintain position (*Figure 1b*)

We have used the submucosal mesenteric pedicle graft in three patients considered to have tenuous aortic stump closures due to an inadequate length of healthy aortic wall below the level of the renal arteries During the same period (36 months), the unit has been referred 11 other infected aortic grafts for excision but, in these, aortic stump closure was considered to be secure and a mesenteric pedicle graft was not employed The perioperative mortality for these 14 patients was 14 per cent (two patients) and at a minimum follow-up of 12 months there has been no incidence of aortic stump rupture. Abdominal CT scans have been performed routinely at 12 months after operation with no evidence of false aneurysm formation.

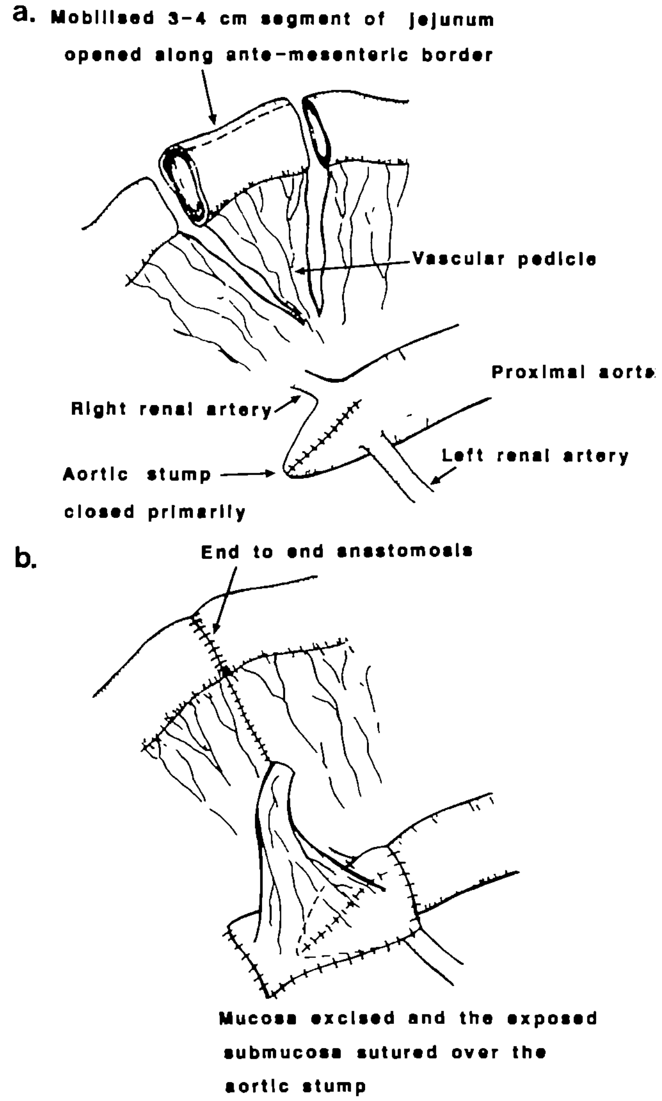
a.
Mobilised 3-4 cm segment of jejunum opened along ante-mesenteric border
Vascular pedicle
Proximal aorta
Right renal artery
Left renal artery
Aortic stump closed primarily
b.
End to end anastomosis
Mucosa excised and the exposed submucosa sutured over the aortic stump

Figure 1 *The technique used to create a submucosal mesenteric pedicle graft showing* **a** *the mobilization of the jejunal segment and* **b** *the pedicle, denuded of mucosa, sutured over the aortic stump*

We believe that the submucosal mesenteric pedicle graft, a highly vascular, absorptive tissue, is a useful adjunct in ensuring secure aortic stump closure

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Blood flow in diabetics with foot lesions due to 'small vessel disease'

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Blood flow was measured in the feet and toes of 23 diabetics, 7 controls and 6 non-diabetic neuropathic controls, using venous occlusion plethysmography. All of the diabetics showed a characteristic flow abnormality with mild hyperperfusion of the foot at rest but impaired peak flow following arterial occlusion. When the diabetics were subdivided into those with 'small vessel disease', those with neuropathic ulceration and those with neuropathy but no ulceration, the groups had remarkably comparable blood flows, except that peak great toe blood flow was rather lower in small vessel disease. In small vessel disease, the combination of high resting blood flow and elevated foot venous oxygen saturation suggests that the hyperperfusion is due to arteriovenous shunting. It seems likely that the toe lesions ascribed to small vessel disease were in fact manifestations of severe diabetic neuropathy. The term small vessel disease should be avoided in the context of diabetic foot lesions.

Keywords: Diabetes mellitus, foot blood flow, digital blood flow, venous occlusion plethysmography

It is standard teaching that 'small vessel disease' causes schaemic diabetic foot lesions. The diagnosis is made by exclusion of large vessel disease in patients with non-neuropathic foot lesions, or sometimes when poor results are obtained following reconstruction of the peripheral vessels[1].

Some authors equate small vessel disease with micro-angiopathy, a well-recognized pathological entity[2,3] which is apparently associated with impaired peripheral blood flow[4]. Indeed, in longstanding asymptomatic diabetics maximal peripheral blood flow is impaired, even when the ankle pulses are palpable[5–7].

A high incidence of micro-angiopathy has been found in limbs amputated for gangrene[2,8,9] but it is clear that amputations of this nature are usually performed for large vessel disease. Attempts to confirm that small vessel disease contributes to ischaemia have proved unsuccessful[10,11].

There is no doubt that diabetes causes accelerated atherosclerosis[12–15], which affects more distal vessels than does non-diabetic atherosclerosis[16,17] This is not the same as Monkeberg's sclerosis which is also common in diabetics, the relevance of which is unclear[18]. Atherosclerosis distal to the ankle can be detected by measurement of toe blood pressure[19] and is a variant of large vessel disease that makes the prognosis much worse It is not, however, small vessel disease

Recent work suggests that arteriovenous shunting of blood may contribute to the development of neuropathic ulceration[20–25]. There is evidence that the associated hyperperfusion may actually cause the capillary lesion recognized by pathologists[26].

Thus it seems there is little evidence that small vessel disease causes ischaemic foot lesions. Surprisingly, foot and toe blood flow has never been measured in patients thought to have small vessel disease.

Patients and methods

Thirty-five diabetics and thirteen controls were referred by colleagues for investigation. None of the diabetics had a history of alcoholism or was taking neurotoxic drugs Fourteen of the diabetics had peripheral neuropathy, characterized by absent ankle jerks, abnormal nerve conduction studies (sensory conduction $<40\,\mathrm{m\,s^{-1}}$) and in some cases impaired vibration perception (using a biothesiometer) Seven of these patients had simple neuropathy and the other seven had classical neuropathic ulcers on the soles of their feet In all of these seven patients there were early signs of neuropathic ulceration or frank ulceration in the contralateral foot. All ulcers were healing at the time of study

The remaining 21 diabetics were felt to have small vessel disease by the referring physician. However, 11 had a history of intermittent claudication and impalpable ankle pulses, and one had an ankle pressure index[27] of 0·75 and a toe pressure of 80 mmHg. These patients with large vessel disease were excluded, leaving nine diabetics with small vessel disease.

These nine patients had a history of ischaemic or infective toe lesions resistant to medical and surgical therapy None was considered to be of neuropathic origin There was no history of cold sensitivity In all cases the ankle pressure index was >0·85 and the systolic toe pressure was >90mmHg. Although they were not considered to have neuropathic symptoms, the ankle jerks were absent in all nine cases. Nerve conduction studies were subsequently performed

Five of the diabetics had maturity onset disease and were taking oral hypoglycaemic agents. The remaining 18 patients were insulin dependent The haemoglobin A was similar in all three groups on the day of study (small vessel disease 11·9±2·8 per cent; neuropathic ulceration 9·9±3·0 per cent, diabetic neuropathy 9·9±2·2 per cent (mean±s.d)

Six non-diabetics with neuropathy were studied. The cause of the neuropathy was alcoholism (two patients), congenital neuropathy (one patient), chronic Guillain–Barré syndrome (one patient) and idiopathic neuropathy (two patients).

There were seven healthy non-diabetic controls.

Informed consent was obtained from all subjects by the first author. The study was approved by the Ethical Committee of The Queen's University of Belfast.

Blood flow

All measurements were made with the patients lightly clad and supine in a heat chamber at a mean temperature of 23·5 (range 23–24°C) The diabetics were instructed to take their normal insulin or hypoglycaemic agents and normal meals. A small snack was provided during plethysmography at the usual time for each individual patient Blood sugar levels were not checked, but urine sugar was not detected before or after the study in the insulin-dependent diabetics

Where possible, both feet and both great toes were studied In two patients with small vessel disease one foot and great toe were not studied because of involuntary muscle spasm which caused repeated movement artefacts In five other cases with small vessel disease, a single great toe was not studied because the great toe was severely deformed (four cases) or the great toe had been amputated (one case). During the early part of the study only one toe plethysmograph was available (control, four cases; non-diabetic neuropathy, two cases).

Foot blood flow was measured by venous occlusion plethysmography using water-filled plethysmographs maintained at

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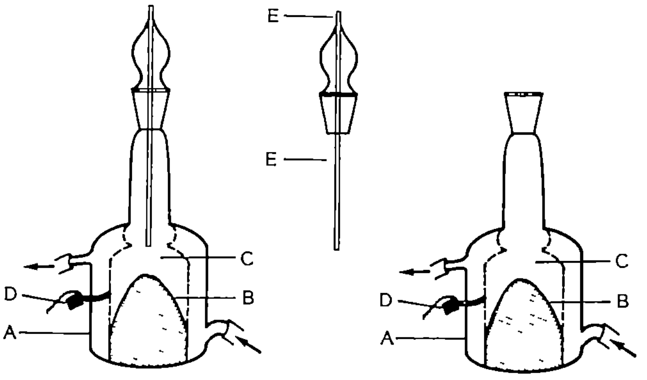

Figure 1 *Plethysmograph for the measurement of great toe blood flow. A, water-perfused outer jacket; B, 50 μm gauge Platilon toe stall; C, inner chamber filled with 95 per cent alcohol, D, entry port to inner chamber for calibrating syringe and thermocouple; E, chimney continuous with upper end of inner chamber C*

32°C[28] Standard adult sphygmomanometer cuffs were applied around the ankles close to (2–3 mm) but not touching the plethysmograph Volume changes were monitored using Grass volumetric transducers (BT5A*) and a Devices M8† pen recorder. Resting flow was measured over a 5-min control period. A collecting cuff pressure of 60 mmHg[29] was used for all measurements. The cuffs were inflated for 15 out of every 20 s. Then a 5-mm period of arterial occlusion was produced by inflating a pressure cuff at the ankle to 220 mmHg The subsequent reactive hyperaemia was recorded, the maximum flow during the recovery period being taken as the 'peak flow'. A collecting cuff pressure of 45 mmHg was used for the initial flow measurement and subsequent measurements were made at a pressure of 60 mmHg. The whole procedure was then repeated and results were calculated from the greater value of peak flow (this usually followed the second period of arterial occlusion)

A modified, light, small-scale version of the conventional plethysmograph was blown in glass specifically for the measurement of great toe blood flow (*Figure 1*). The technical specifications are described in detail elsewhere[30]. This consisted of a sealed outer water jacket, perfused constantly by water at 32°C. The inner chamber contained a 50 μm gauge Platilon‡ toe stall into which the distal phalanx of the great toe was inserted The space between the toe stall and the plethysmograph was filled with alcohol, which obliterates the dead space around the toe. Thus, changes in toe volume <0 05 ml are readily measured by the volumetric transducers and recorded on a pen recorder. The apparatus was calibrated by addition of 0 1 ml aliquots of alcohol from an integral glass syringe, the temperature of the alcohol being constantly monitored using a thermocouple

A purpose-built digital collecting cuff manufactured from Velcro® and rubber was applied to the proximal phalanx of the great toe. To prevent bulging of the toe stall below the water jacket, plastic discs were cut to closely fit the great toe and then taped to the underside of the apparatus The experimental protocol was similar to that for the feet.

Great toe systolic pressure was measured by applying half-inch rubber on Velcro cuffs around the base of the digit. Using a photoplethysmograph, the point at which systolic flow could first be detected was recorded during cuff deflation. The mean of four readings was taken. A standard sphygmomanometer cuff was applied at the ankle and the systolic pressure in the posterior tibial artery was recorded using a 10 MHz Doppler probe. The mean of four recordings was taken The mean brachial pressure was recorded in a similar fashion and the ankle pressure index (ankle pressure: brachial pressure) calculated.

Venous oxygen saturation

Samples of venous blood from dorsal veins on the foot and hand were taken without congestion at the end of the experimental period and immediately analysed on a Co-oximeter 282 (Instrumentation Laboratory Ltd).

Statistical analysis

In all possible cases, both feet and both great toes were studied (se above). Comparison of the left and right foot (Spearman ran correlation coefficient. resting $r_S = 0\ 73$, peak $r_S = 0{\cdot}75$) and toe (restin $r_S = 0\ 64$, peak $r_S = 0\ 58$) flow values showed a good correlation betwee the two sides. It was not possible to use results from both feet/toe (where both had been measured) in a single statistical analysis as thi would have invalidated the assumption of independence. Therefore, mean flow value was calculated for these patients. In those cases wher one foot or toe was not studied, the flow value from the other side wa used in the analysis

Heterogenicity of the results necessitated the use of non-parametri analyses (diabetics *versus* non-diabetics: Mann–Whitney *U* test between diabetic subgroups: Kruskal–Wallis one-way ANOVA).

Results

There was an excess of male patients in the small vessel diseas group and in the controls. The groups were comparable in term of age. In addition, the three diabetic groups had a comparabl range of disease duration and glycaemic control, as assessed b the level of haemoglobin A in their blood (*Table 1*).

There was no difference in ankle pressure index between th groups but the systolic toe pressure was lower in the small vesse disease group (Kruskal–Wallis one-way ANOVA, $P = 0{\cdot}006$).

Resting foot blood flow was similar in all three diabeti groups and was significantly greater than in either of the tw control groups ($P = 0{\cdot}003$) (*Table 2*). However, peak foot bloo flow was significantly lower in the diabetics ($P = 0{\cdot}002$). Agai no significant difference was detected between the diabeti subgroups.

In the great toe, resting flow did not differ significantl between any of the groups studied (*Table 3*). On the other hand peak great toe flow was rather lower in the patients with smal vessel disease than in any of the other groups though th difference was not significant. The increase in toe flow i response to ischaemia was significantly lower in the small vesse

Table 1 *Comparison of the five groups*

	SVD	NU	DN	NDN	Control
Sex					
Male	8	4	4	2	6
Female	1	3	3	4	1
Age (years)	58·1	57·4	53·9	59·3	63 4
s.d	10 6	9·4	9·2	12·4	8 2
Disease duration (years)	20·2	11·3	20 6	—	—
s d.	11·1	9·1	12·9	—	—
Haemoglobin A (%)	11·9	9·9	9·9	—	—
s d	2·8	3·0	2·2	—	—
Ankle pressure index	1·02	1·06	1·05	1·05	1·15
s d	0·14	0 1	0·18	0 13	0 21
Toe pressure (mmHg)	107	128	143	123	130
s d.	15·6	14·6	4·5	20·8	16 4

SVD, small vessel disease; NU, neuropathic (diabetic) ulceration; DN diabetic neuropathy; NDN, non-diabetic neuropathy. Except for sex o patient, the values are mean and s d.

Table 2 *Foot blood flow in the five groups*

	Resting	Peak	Increase	Recovery time
SVD	3·3 (1·3)	6·7 (2·1)	3·4 (1 6)	3·3 (1·5)
NU	3·3 (1 1)	5·9 (2·5)	2 6 (1 9)	2·7 (1 1)
DN	3·2 (1·2)	7·4 (3 0)	4 2 (2·3)	2·9 (1·6)
NDN	1·9 (0·5)	9·4 (1 9)	7·5 (1·9)	3·3 (1·1)
Control	2·2 (0·6)	9·8 (2 6)	7 6 (2 3)	3 4 (1·8)

Mean measurements are given in ml $100\,\mathrm{ml}^{-1}\,\mathrm{min}^{-1}$; values i parentheses are s.d. SVD, small vessel disease; NU, neuropathi (diabetic) ulceration; DN, diabetic neuropathy; NDN, non-diabeti neuropathy disease group than in the other diabetics ($P=0·005$) in both absolute and percentage terms.

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* *Grass volumetric transducers are manufactured by Grass Medical Instruments, Massachusetts, USA;* † *Devices M8 pen recorders are manufactured by Ormed Ltd., UK, and* ‡ *Platilon toe stalls are manufactured by PRA Plastics Ltd , UK. Velcro® is a trademark of Selectus Ltd., UK*

Venous oxygen saturation in the hand was similar in all groups (*Table 4*). However, foot venous oxygen saturation was significantly higher in the diabetics (Mann–Whitney U test, $P<0·0001$) (*Table 4*). The venous oxygen saturation was highest in those diabetics with small vessel disease and lowest in the patients with uncomplicated neuropathy (Kruskal–Wallis one-way ANOVA, $P=0·04$).

Table 5 shows the incidence of various complications in the five groups of patients and it can be seen that these are all maximal in the small vessel disease group. Objective measurement of neuropathy (*Table 6*) indicated that motor and sensory nerve conduction and vibration perception thresholds were most severely abnormal in the small vessel disease group despite the absence of clinical signs or symptoms.

Table 3 *Toe blood flow in the five groups*

	Resting	Peak	Increase	Recovery time
SVD	8·6 (5·1)	15·6 (8·7)	7·0 (3·9)	3·8 (1·1)
NU	7·0 (3·6)	21·1 (9·3)	14·1 (5·9)	3·5 (1·2)
DN	8·1 (6·0)	22·9 (16·5)	14·9 (10·8)	3·7 (1·4)
NDN	6·6 (2·5)	25·0 (8·7)	18·4 (7·8)	2·9 (1·4)
Control	7·1 (4·1)	24·5 (10·4)	17·5 (7·1)	3·2 (1·1)

Mean measurements are given in ml 100 ml^{-1} min^{-1}; values in parentheses are s.d. SVD, small vessel disease; NU, neuropathic (diabetic) ulceration; DN, diabetic neuropathy; NDN, non-diabetic neuropathy

Table 4 *Venous oxygen saturation (%) in the five groups*

	SVD	NU	DN	NDN	Control
Hand O_2 haemoglobin	79·3	77·2	83·3	82·1	76·2
s.d	8·7	10·7	12·7	15·1	14·7
Foot O_2 haemoglobin	89·9	87·4	81·7	72·3	73·9
s.d.	3·0	6·2	7·8	13·1	8·0

SVD, small vessel disease; NU, neuropathic (diabetic) ulceration; DN, diabetic neuropathy, NDN, non-diabetic neuropathy Values are mean and s.d.

Discussion

All groups of patients were comparable in terms of age and the patients in the three diabetic groups all had a comparable range of disease duration and glycaemic control. The most marked difference between the groups was the preponderance of men in the small vessel disease group. The diagnosis of small vessel disease is rather unsatisfactory. These patients had ischaemic toe lesions (in six cases requiring amputation). They did not have neuropathic ulceration or large vessel disease. By a process of exclusion their attending physicians had concluded that the cause of these toe lesions was small vessel disease. Our study calls into question the validity of this conclusion; nevertheless, it was made before entry into the study. In all cases the ankle jerks were absent and nerve conduction studies were abnormal. In five of the nine patients the vibration perception threshold was also abnormal[31]. However, we did not find vibration perception threshold very useful as it was normal in six of the seven patients with neuropathic ulceration and five of the seven patients with neuropathy.

When we commenced the study we expected to find reduced

Table 5 *Diabetic complications in the five groups*

	SVD	NU	DN	NDN	Control
Number of patients	9	7	7	6	7
Retinopathy*	8	3	1	—	—
Nephropathy†	3	2	0	—	—
Abnormal nerve conduction studies	9	7	7	6	—
Abnormal vibration perception threshold (corrected for age)	5	1	2	—	—

* Background retinopathy, assessed by ophthalmoscopy, † proteinuria and/or serum creatinine > 120 μmol l^{-1}; SVD, small vessel disease; NU, neuropathic (diabetic) ulceration, DN, diabetic neuropathy; NDN, non-diabetic neuropathy

Table 6 *Vibration perception threshold and nerve conduction velocity in the diabetic groups*

	Age (years)	VPT	Expected 95% confidence limit VPT	Motor conduction velocity (m s^{-1})	Sensory conduction velocity (m s^{-1})
Small vessel disease	56	47	36	35	33
	70	39	50	27	32
	68	17	45	33	29
	48	32	32	0	0
	74	27	>50	35	38
	60	32	40	34	34
	43	47	27	22	0
	52	42	33	37	37
	46	37	30	42	38
Diabetic neuropathic ulceration	54	12	34	36	35
	60	18	40	38	40
	46	21	30	35	40
	67	29	44	41	38
	72	32	>50	36	38
	49	19	32	33	39
	54	45	35	34	33
Diabetic neuropathy	48	19	32	34	38
	55	37	35	39	40
	50	23	32	33	36
	52	31	33	37	39
	49	35	32	29	32
	74	27	>50	40	38
	49	30	32	30	31

VPT, vibration perception threshold

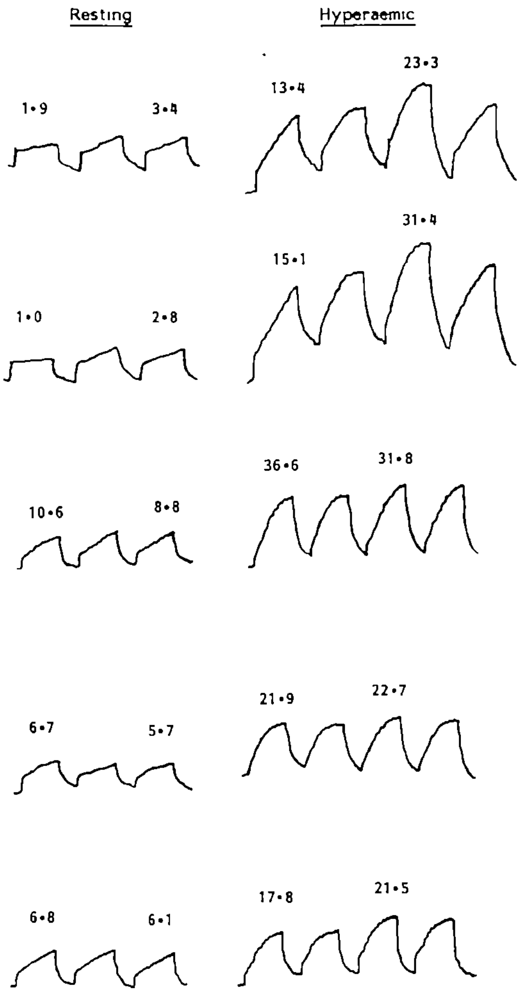

Figure 2 *Resting and peak toe blood flow tracings in five different subjects. The slope of the trace indicates the flow (in ml 100 ml^{-1} min^{-1}). Even when very high flow values are obtained, accurate measurement of the flow rate is possible. Reactive hyperaemia in response to 5 min of arterial occlusion is clearly seen (peak blood flow)*

toe blood flow in the patients with small vessel disease. Thus the result was something of a surprise. In retrospect, it is clear that this group have severe neuropathy. However, other than absent ankle jerks, no clinical symptoms or signs of neuropathy had been elicited and the physicians in charge of their care (and ourselves) had not considered that neuropathy played a significant role in the aetiology of their foot lesions.

The validity of venous occlusion plethysmography has been extensively reviewed[32,33] and it is recognized that water displacement plethysmography is the gold standard against which other methods must be judged[34].

Toe plethysmography is difficult to perform and not widely accepted However, our new apparatus, which is described in detail elsewhere[30,35], clearly produced satisfactory recordings (*Figure 2*). Venous congestion due to the relatively small capacity of the toe was not usually a problem. Between two separate runs of ten flow measurements at 30-min intervals on the same patient, the apparatus has a coefficient of variation of 8·7 per cent (s.d 0 99 per cent). This is considerably less than the normal variation that occurs due to changes in sympathetic tone (coefficient of variation 20 per cent, s.d. 1·8 per cent)[35].

The modestly, but significantly, higher resting foot blood flow in the diabetic patients compared with the control patients is interesting. Christensen[18], using a similar technique, found comparable differences in foot blood flow in asymptomatic diabetic patients and controls. On the other hand, Archer[36] using strain gauge plethysmography reported very much higher flows in patients with diabetic neuropathy, especially in the great toe. Archer positioned the collecting cuffs in a similar position to that used by us The differing results may reflect th selection of a different group of subjects or could perhaps be du to the positioning of the strain gauge. Our plethysmograp measures total toe blood flow. The strain gauge measures flov only in the segment of toe under the instrument It is wort remembering that there are many arteriovenous channels and rich capillary bed at the base of the nail—the usual position o the strain gauge.

However, even the small increase in resting flow seen in th present study is of interest since both local and genera environmental conditions were carefully controlled. Recen work has suggested that, in diabetic neuropathic ulceration arteriovenous shunting may occur due to involvement o peripheral sympathetic vasomotor nerve fibres[23,24,26], though causal relationship has not been established. Feature suggestive of capillary overperfusion occur early in the course o diabetes mellitus[37,38].

The measurements of venous oxygen saturation seen in th present study would tend to support the arteriovenous shuntin theory. The significantly higher values for foot venous oxyge saturation in the three diabetic groups could be associated wit preferential flow of blood through open non-nutrien arteriovenous connections. The resultant degree of bypassin of the nutrient capillary exchange vessels could produc apparently ischaemic tissue in the presence of perfectly adequat overall blood flow.

However, the increased venous oxygen saturation in the foo could also be explained if blood flowed through the norma capillary pathway but oxygen diffusion was impaired along th capillary-to-tissue cell pathway Again ischaemic tissu damage could result even in the presence of adequate regiona blood flow. The present study cannot distinguish between thes two possibilities. However, it is unlikely that the capillary lesio in longstanding diabetes represents a barrier to diffusion when i is associated with increased capillary permeability[39–41]

In clinically significant large vessel disease, resting bloo flow may be normal. Functional stressing of the circulation i required to reveal abnormalities. Following 5-min arteria occlusion, the peak foot flows after release were significantl decreased in all the diabetic groups. A significant decrease i peak toe flow following occlusion was present only in the smal vessel disease group. These low peak flows are unlikely to be du to extensive obstructive arterial disease, in view of the norma ankle:brachial ratio in all groups (and the normal toe pressure in the neuropathic diabetics). However, great care must b exercised in interpreting ankle pressure results in diabetics sinc their more rigid vessels may produce erroneously high pressur recordings.

In the patients with small vessel disease several finding might suggest a degree of occlusive vascular disease, particularl in the region between the ankle (where the pressure is normal) an the toe (where a modest but significant drop in systolic pressur was observed in small vessel disease). Faris has interpreted thi ankle–toe pressure gradient, which he observed mainly i neuropathic subjects with foot lesions, as evidence of metatarsa atherosclerosis[42]. However, resting great toe blood flow wa higher in the small vessel disease group than in any of the othe groups. If this and the elevated venous oxygen saturation ar indeed due to arteriovenous shunting, then the drop in pressur from ankle to toe may simply be due to a loss of periphera resistance. Peak great toe blood flow was reduced in small vesse disease but the highest flow was usually the first or second flo recorded after release of the occluding cuff and the pattern o recovery of flow to resting levels was not typical of occlusiv vascular disease. In healthy subjects and in the diabetics wit small vessel disease the first or second flow value was usuall the highest and recovery to resting flow levels was rapid. I atherosclerosis the peak flow is delayed and recovery i prolonged (*Figure 3*)[43].

The impairment in peak flow might be because of a deficiency in local vasodilator synthesis. Abnormal prostacycli production[44], and a reduced histamine response[45] have bee

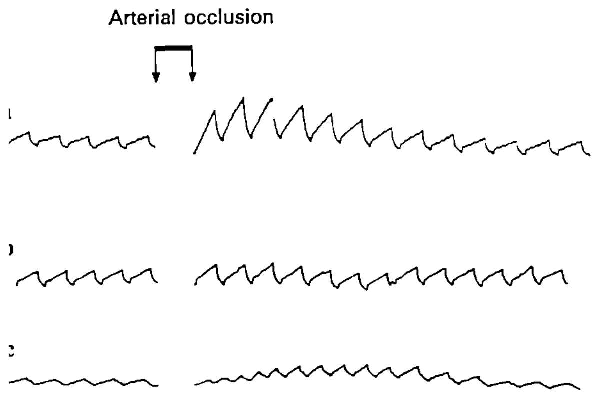

Figure 3 *Resting and peak toe blood flow tracings in* **a** *a control,* **b** *a iabetic with small vessel disease;* **c** *a patient with atherosclerotic ischaemia. Normal resting blood flow is indicated by the slope of the recordings on the left. In controls and in small vessel disease, after 5 min of arterial occlusion, peak flow is achieved immediately the occluding cuff is released and the flow rate rapidly falls to normal. This is quite different from the pattern in atherosclerosis*

described in diabetics. Since the patients with small vessel disease have more severe retinal, renal and neural disease, it would not be surprising if their vascular endothelium was similarly affected. Peak blood flow is not impaired after sympathectomy[46], and so the presence of autosympathectomy due to diabetic autonomic neuropathy is unlikely to be a contributing factor.

Perhaps the most surprising find in this study was the severely impaired motor and sensory nerve conduction and vibration perception in the small vessel disease group of patients. In view of the problems they had all experienced with foot lesions, one can only conclude that this group must represent an advanced stage of diabetic neuropathy. Gangrenous neuropathic toe lesions are illustrated by Faris in a recent book on the management of the diabetic foot[47]. Our patients with small vessel disease are clearly similar

In conclusion, we have found no evidence that small vessel disease is a separate entity; rather this term has been applied to a group of patients with diabetes complicated by multisystem disease. Peripheral blood flow patterns in these patients are compatible with severe autonomic neuropathy. Significant sensory and motor neuropathy can be demonstrated by objective measurements in all cases. While a minor degree of occlusive arterial disease distal to the ankle may be present in these patients, we do not believe that this contributes significantly to the development of their foot lesions.

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Case report

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Kikuchi's disease simulating acute appendicitis

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The syndrome now known simply as Kikuchi's disease was first described individually by Kikuchi[1] and Fujimoto *et al.*[2] in 1972. They described severe necrotizing lymphadenitis in Japanese patients presenting with tender cervical lymphadenopathy. This paper describes this condition involving only the mesenteric lymph nodes, simulating appendicitis.

Case report

A 29-year-old Asian women presented with a 2-day history of right iliac fossa pain, malaise, fever and vomiting. There were no urinary or gynaecological symptoms and no previous history of similar complaints, although her past medical history included laparotomy during childhood for unknown reason.

On examination she was flushed with a tachycardia of 100 beats/min and in sinus rhythm. Pyrexia of 38·5°C was noted and there was no cervical lymphadenopathy. Abdominal examination revealed an upper midline scar and tenderness with guarding in the right iliac fossa. Vaginal examination was normal. Rectal examination showed she was tender on the right side. Routine investigations showed Hb 12·3, WBC 5·0 (differential 0·8 per cent lymphocytes, 0·4 per cent monocytes, 3·8 per cent granulocytes). A mid-stream urine was acellular with no organisms seen on microscopy.

As the nature of her previous surgery was unknown, a presumptive diagnosis of acute appendicitis was made. Laparotomy through a grid iron incision revealed florid lymphadenopathy of the mesenteric nodes of the terminal ileum and caecum with haemorrhagic areas in the overlying omentum. The terminal ileum and small bowel, caecum and ovaries were normal. The appendix was absent, presumably following previous laparotomy. One of the lymph nodes was removed for histological and microscopic examination before abdominal closure. Her postoperative course was uneventful with her fever settling on the second postoperative day.

During the postoperative period blood was taken for blood culture, double stranded DNA, rheumatoid factor, *Yersinia*, *Mycoplasma* and *Toxoplasma* and viral serology and all proved negative. Lymph node culture and staining for acid alcohol-fast bacillus was negative.

Histology

There was a necrotizing process which predominantly affected the medulla of the lymph node extending into the cortex, involving 90 per cent of the node. This was characterized by areas of cellular proliferation, followed by apoptotic (single cell) death, culminating in total cell death associated with zones of eosinophilic fibrinoid material and scattered nuclear dust. Remaining germinal centres were present at the periphery of the node. Immunocytochemical staining with UCHLI and MB2, antibodies to the T200 and CD4S antigens of T and B lymphocytes respectively, showed that the majority of the proliferating cells were UCHLI positive, i.e. they were T cells; there was also a marked T reaction product lying free in the necrotic areas.

These are the features for necrotizing lymphadenitis of Kikuchi's disease.

Discussion

The aetiology of Kikuchi's syndrome is unknown and many causes have been postulated, among which an infection with either a virus, *Toxoplasma* or *Yersinia* have been included. However, none have been proved to be the true aetiological agents. The disease itself usually presents in females in the second and third decades and whilst initially confined to Japanese, the condition has now been described in Caucasians and Asians[3,4].

The classical presentation is of painful, tender cervical lymphadenopathy, associated with pyrexia and frequently arthralgia and rash. The diagnosis is usually made by excision biopsy to exclude either the clinical diagnosis of tuberculosis or lymphoma. There is usually a polymorphonuclear leucopenia. Histologically the nodes have to be distinguished from lymphoma, bacterial lymphadenitis, lymphadenopathy associated with systemic lupus erythematosus and vascular nodal infarction.

In the past up to 40 per cent of early cases of Kikuchi's disease were wrongly diagnosed as lymphoma. Several of the features described both histologically and clinically are suggestive of Kikuchi's syndrome and we believe that to date this is the first documented case of one presenting simulating acute appendicitis.

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Pulmonary microembolization in experimental aortic surgery

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Pulmonary dysfunction frequently follows major surgery and has many features identical to 'shock lung'. A porcine model of aortic surgery is described in which ^{111}In-labelled platelet kinetics were related to subsequent pulmonary function. In 14 pigs, standardized aortic surgery resulted in reproducible shock and a 50 per cent mortality at 3 days. Cardiac output fell from $2{\cdot}3 \pm 0{\cdot}2$ to $1{\cdot}0 \pm 0{\cdot}1$ litres min^{-1} following removal of the aortic clamp and mean platelet and leucocyte counts fell from 437 ± 48 to $252 \pm 39 \times 10^9$ litres^{-1} and $21{\cdot}7 \pm 1{\cdot}5$ to $12{\cdot}9 \pm 1{\cdot}2 \times 10^9$ litres^{-1} respectively ($P < 0{\cdot}01$). Aggregate levels in inferior vena caval blood were maximal at this time and radiolabelled platelets accumulated in the lung with a rise in pulmonary vascular resistance. Alveolar–arterial oxygen difference subsequently increased from initial values of $13{\cdot}7 \pm 2{\cdot}0$ to $23{\cdot}4 \pm 3{\cdot}5$ mmHg ($P < 0{\cdot}01$) following resuscitation and to $32{\cdot}5 \pm 3{\cdot}4$ mmHg at 3 days following surgery ($P < 0{\cdot}01$). This clear sequence suggests that pulmonary platelet microembolization occurs during surgical shock and may be responsible for subsequent pulmonary dysfunction.

Keywords: Blood platelets, shock, pulmonary dysfunction

Postoperative pulmonary dysfunction has been classified as moderate or severe in approximately one-third of patients after major abdominal surgery, and pulmonary failure is the most frequent cause of morbidity and mortality[1]. More commonly referred to as 'postoperative hypoxia' this condition is extensively described after both upper abdominal and major vascular reconstruction[2,3]. The clinical features in severe cases are identical to the syndrome described as 'shock lung' or adult respiratory distress syndrome with diffuse pulmonary opacification and severe pulmonary venous admixture[4]. It therefore seems plausible that the basic pathology and aetiology may be similar.

Microaggregates composed of platelets, fibrin or leucocytes have been detected in venous blood during both shock and surgery and may potentially embolize to the lungs causing this damage[4–6]. Such pulmonary microembolization has been demonstrated in both experimental and clinical shock and may be the common pathway leading to pulmonary damage following all forms of shock and major surgery[7,8]. To investigate whether microembolization of the lungs does occur during aortic surgery, we developed an experimental model which permitted detailed measurement of circulatory haemodynamics, platelet kinetics and pulmonary function both during and 3 days after standardized aortic surgery.

Methods

Surgical shock model

Fourteen female pigs (20–30 kg) were anaesthetized by Brietal infusion (10 mg kg^{-1} min^{-1}), endotracheal intubation and intermittent positive pressure ventilation. Arterial and Swan–Ganz catheters were inserted into the carotid and internal jugular vein via a small incision in the right neck, allowing arterial and mixed venous blood samples and measurement of pulmonary arterial pressure, pulmonary wedge pressure and cardiac output. Following full midline incision, the small bowel was exteriorized for 30 min while the retroperitoneal dissection was performed. The infrarenal aorta was then clamped for 90 min so that the whole procedure mimicked clinical aortic surgery as closely as possible. On removal of the aortic clamp, shock developed and was allowed to persist for a period of 60 min before resuscitation with a rapid infusion of 30 mg kg^{-1} intravenous Haemaccel® to restore baseline pulmonary capillary wedge pressures. Anaesthesia was then reversed and 500 ml Haemaccel infused every 12 h until oral fluids were resumed. Surviving animals were re-anaesthetized 3 days postoperatively and all the studies listed below were repeated before the animal was killed using intravenous phenobarbitone.

Measurements during and following surgery

All the following measurements were performed at four intervals during the course of major surgery and then once postoperatively, that is (i) after stabilization on anaesthesia but before the aorta was clamped (induction), (ii) after full laparotomy, small bowel exteriorization, retroperitoneal dissection and 90 min of aortic clamping (surgery), (iii) 60 min after removal of the aortic clamp (shock), (iv) after 30 min of resuscitation (resuscitation) and (v) in surviving animals 3 days postoperatively (3 days).

Indices of shock

Mean arterial blood pressure, pulmonary arterial pressure and pulmonary capillary wedge pressure were monitored using data recorded from the arterial and Swan–Ganz catheters. Cardiac output was calculated by a cardiac output computer (Model 9520, Edwards Labs, Santa Ana, California, USA) using the thermodilution method[9]. Pulmonary vascular resistance index (PVRI) was calculated from the mean pulmonary arterial pressure (MPAP), the mean pulmonary capillary wedge pressure (PCWP) and the cardiac index (CI) using the formula:

$$\text{PVRI} = \frac{\text{MPAP} - \text{PCWP}}{\text{CI}}$$

Blood cell kinetics

Platelet and leucocyte counts at each sampling time were measured by Coulter counter (Model S)† and corrected to the initial haematocrit. On the day before surgery autologous platelets were labelled with 100 μCi ^{111}In-oxine and re-injected to allow circulating platelet radioactivity and radiolabelled platelet accumulation in the lung to be measured. Circulating platelet radioactivity was estimated by measuring radioactivity of 2 ml of blood in a well crystal and expressed as counts s^{-1} g^{-1}. The radiolabelled platelet content of the lungs was measured by counting radioactivity over both lung fields using a highly collimated scintillation probe and ratemeter (Eberline Instruments). The probes were centred over the seventh rib anteriorly, midway between the

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† The Coulter counter is manufactured by Coulter Electronics, Hialeah, France

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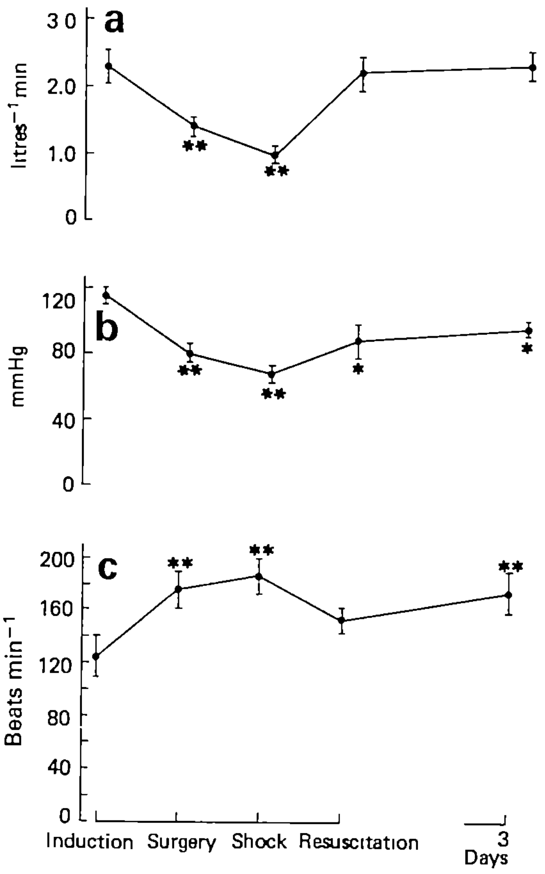

Figure 1 *Surgery involving bowel exteriorization, retroperitoneal dissection and aortic clamping produced a fall in cardiac output to 1·0±0·1 litres min*$^{-1}$ (**a**), *a similar fall in blood pressure* (**b**) *and a tachycardia* (**c**). *These all improved on resuscitation but even in survivors tachycardia returned at 3 days. Values are mean±s.e.m.* *$P<0{\cdot}05$, **$P<0{\cdot}01$

midline and lateral limits of the rib cage and angled 20° superiorly to eliminate emissions from the liver and spleen. Radioactivity over the head as a reference area was measured and lung platelet uptake expressed as a ratio of pulmonary over head radioactivity.

Venous microaggregates

Aggregates in venous blood were estimated by measuring the slope of the screen filtration pressure curve of vena caval blood using the modified Swank technique for *in vivo* aggregates[4]. A nickel filter of 2·4 mm diameter and pore size 20 μm square and deep was primed by the passage of 3 ml normal saline at 37°C. Using a plastic syringe and a 21 gauge needle, 3·25 ml of blood was obtained from the inferior vena cava by direct venepuncture and passed through the filter at a constant flow rate of 0·4 ml s^{-1} by syringe pump. The pressure proximal to the filter was measured by strain gauge transducer and recorded graphically as the screen filtration pressure test curve. The filter was finally flushed with a further sample of saline and preserved in buffered 0·5 per cent gluteraldehyde before examination by scanning electron microscopy.

Pulmonary function

The standard Clark and Severing Haus electrodes (Instrumentation Laboratory) were used for arterial and mixed venous blood gas analysis. Pulmonary arteriovenous shunt and alveolar–arterial oxygen difference were calculated using a computer program (Apple Ltd., UK) based on the following standard formulae[10]. The inspired oxygen tension (P_{I,O_2}), arterial carbon dioxide tension (P_{a,CO_2}), fraction of inspired oxygen (F_{I,O_2}) and respiratory exchange ratio (R) were used to calculate the ideal alveolar oxygen tension (P_{A,O_2}) from the equation:

$$P_{A,O_2}=P_{I,O_2}-\frac{P_{a,CO_2}(1-F_{I,O_2}[1-R])}{R}$$

The alveolar–arterial oxygen difference was then calculated using the ideal alveolar oxygen tension (P_{A,O_2}) and arterial oxygen tension (P_{a,O_2}) from the alveolar air equation:

$$\text{Alveolar–arterial oxygen difference}=P_{A,O_2}-P_{a,O_2}$$

The end capillary oxygen content (C_{c,O_2}) was derived from ide alveolar oxygen tension and haemoglobin. The arterial oxygen conte (C_{a,O_2}) and mixed venous oxygen content (C_{v,O_2}) were then used t calculate pulmonary arteriovenous shunting where

$$\text{Percentage shunt}=\frac{C_{c,O_2}-C_{a,O_2}}{C_{c,O_2}-C_{v,O_2}}\times 100$$

Statistical analysis

All data were expressed as mean±s.e.m. and the paired Wilcoxon te was used to compare results at each time interval with the initial valu before surgery.

Results

The severity of shock was such that 7 of the 14 animals die within 16 h of surgery, leaving 7 surviving for further studies at days.

Indices of shock

The initial cardiac output of 2·3±0·2 litres min^{-1} fe progressively to 1·4±0·2 litres min^{-1} during aortic clamping an to 1·0±0·1 litres min^{-1} during the shock interval after remova of the clamp ($P<0{\cdot}01$) (*Figure 1a*). Resuscitation restore cardiac output to 2·2±0·2 litres min^{-1} which was maintaine 3 days postoperatively. Similarly, the mean arterial pressur fell from 116±6 mmHg at induction to the lowest reading o 70±6 mmHg after declamping ($P<0{\cdot}01$), but recovered t 90±9 mmHg after resuscitation (*Figure 1b*). A tachycardia als developed during surgical shock, recovering after resuscitatio but returning to significantly higher values in survivors at days ($P<0{\cdot}01$) (*Figure 1c*).

Blood cell kinetics

The mean platelet count fell from initial levels of 437±48 t 332±43×10^9 litres^{-1} during aortic clamping and to 277± 34×10^9 litres^{-1} during shock ($P<0{\cdot}01$) (*Figure 2a*). Thi continued to fall after resuscitation to 252±39×10^9 litres$^-$ and postoperatively to only 99±13×10^9 litres^{-1} in survivors a 3 days ($P<0{\cdot}01$). Circulating blood radioactivity, reflectin platelet survival, showed a progressive and almost identical fal confirming that platelet count changes reflected loss o circulating platelets during surgical shock (*Figure 2b*) Leucocyte counts fell in a similar way from 21·7±1·5×10 litres^{-1} to 12·5±1·1 and 12·9±1·2×10^9 litres^{-1} during shoc and resuscitation respectively and then further to 8·8±1·7×10 litres^{-1} at 3 days ($P<0{\cdot}01$).

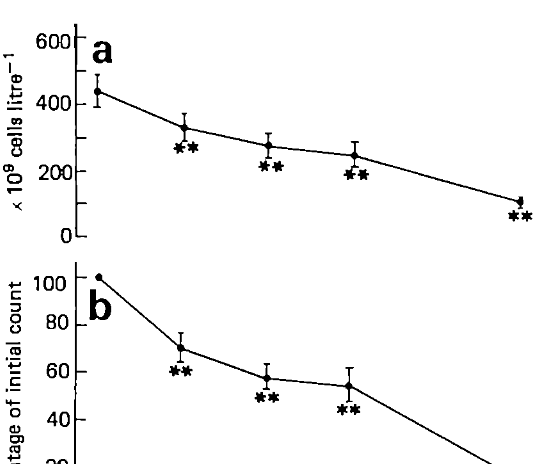

Figure 2 *Surgery produced falls in platelet count* (**a**) *with an almos identical change seen in circulating platelet radioactivity* (**b**). *Values ar mean±s.e.m* **$P<0{\cdot}01$

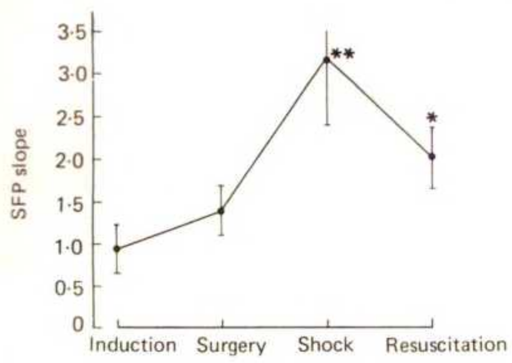

Figure 3 *Changes in screen filtration pressure of inferior vena caval blood indicating circulating aggregates are present following release of the aortic clamp and during resuscitation. Values are mean ± s.e.m.* * $P<0{\cdot}05$, ** $P<0{\cdot}01$

Venous microaggregates

The screen filtration pressure of vena caval blood increased from 1·0 ± 0·3 initially to a maximum of 3·2 ± 0·8 after declamping of the aorta ($P<0{\cdot}01$) (*Figure 3*). It remained significantly elevated at 2·0 ± 0·4 after resuscitation, indicating that microaggregates were still forming in peripheral venous blood. Scanning electron microscopy of screens used to filter 3·25 ml of venous blood from animals before surgery demonstrated few aggregates on the filter surface compared with the many large aggregates, up to 80 μm in diameter, found during shock (*Figure 4*).

Lung platelet uptake

Radiolabelled platelet accumulation in the lung increased progressively when aggregates were detected in venous blood. The pulmonary radioactivity ratio rose to 10·9 ± 1·1 during the shock interval after aortic declamping compared with induction ratios of 8·3 ± 0·6 ($P<0{\cdot}01$) (*Figure 5a*). Postoperatively pulmonary radioactivity remained elevated at 10·8 ± 1·2 but as only seven animals survived to 3 days this rise was no longer statistically significant.

Pulmonary haemodynamics

Pulmonary vascular resistance measured as PVR index was 364 ± 45 dynes. s $\mathrm{cm^{-5}\,m^{-2}}$ on induction. This increased to a peak of 1096 ± 165 dynes. s $\mathrm{cm^{-5}\,m^{-2}}$ after declamping ($P<0{\cdot}01$) (*Figure 5b*). Left ventricular failure played no part in the increased PVRI as pulmonary wedge pressure remained normal or low throughout. Pulmonary arteriovenous shunt was 6·2 ± 0·7 per cent of cardiac output initially and remained relatively unchanged during clamping and declamping. After restoration of cardiac output by resuscitation, shunting more than doubled to 12·9 ± 2·4 per cent with a fall in PVRI (*Figure 5c*) ($P<0{\cdot}01$). In the seven survivors this increased further to 18·9 ± 3·5 per cent by the third postoperative day ($P<0{\cdot}01$).

Pulmonary function

Alveolar–arterial oxygen difference reflected the changes in pulmonary shunt, changing little during surgery and shock from the pre-operative value of 13·7 ± 2·0 mmHg, but rising with pulmonary shunt on resuscitation and restoration of cardiac output to 23·4 ± 3·5 mmHg and further in survivors to 32·5 ± 3·4 mmHg at 3 days ($P<0{\cdot}01$) (*Figure 5d*). Although the pig could compensate for the moderate increase in alveolar–arterial oxygen difference after resuscitation, the greater increase at 3 days was associated with a fall in arterial oxygen tension from 104 ± 6 to 70 ± 4 mmHg ($P<0{\cdot}05$) (*Figure 5e*).

Discussion

This animal model was developed to simulate aortic surgery in patients and allows a unique opportunity to relate changes in pulmonary function with events during surgical shock. Major surgery, including aortic reconstruction, is frequently complicated by impaired pulmonary function which may range in severity from mild postoperative atelectasis to acute respiratory failure[1,5,11]. The severity of shock in our aortic surgery model was confirmed by tachycardia, marked falls in cardiac output and blood pressure in all animals and a postoperative mortality of 50 per cent despite resuscitation. During this shock, platelet and leucocyte counts fell at the same time as platelet aggregates were found on screen filtration pressure measurements. Subsequently, pulmonary platelet radioactivity and pulmonary vascular resistance increased suggesting embolization to the pulmonary vascular bed, probably accompanied by the release of vasoactive substances from platelets. On resuscitation and restoration of cardiac output, intrapulmonary arteriovenous shunting developed with subsequent rises in alveolar–arterial oxygen difference.

The ultimate cause of shock in this model, and throughout surgery in general, remains poorly understood. Tissue trauma probably plays a role and exteriorization of the small bowel produced marked deterioration in these pigs, presumably because of fluid loss or mucosal dysfunction with endotoxin absorption. Portal and systemic endotoxinaemia have been previously observed in a wide range of surgical procedures. Aortic cross-clamping may also be important and reperfusion pulmonary injury is described[12,13]. Almost certainly the circulatory failure seen in this model results from a combination of these known and possibly other as yet unknown influences. The most important difference between our model and clinical major surgery was that fluid resuscitation was not continuous throughout the 'operation' so that the circulatory consequences of these several processes were not masked.

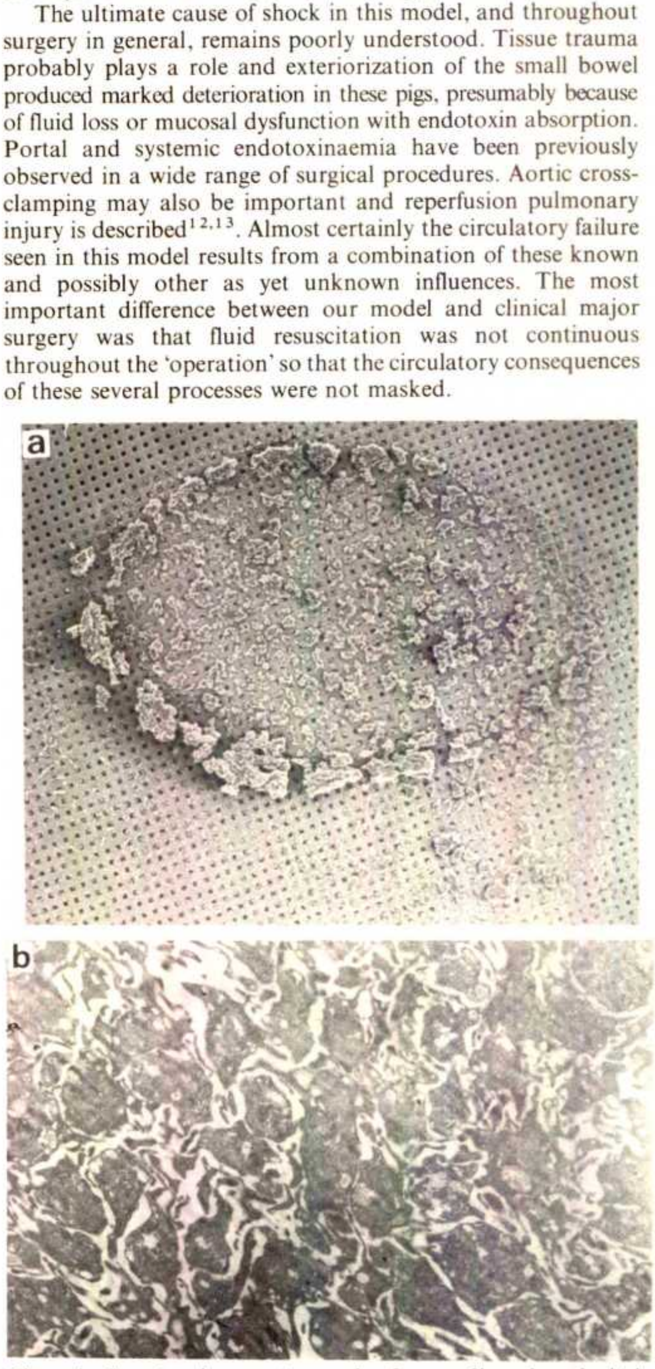

Figure 4 *Scanning electron micrographs of screen filters through which vena caval blood has been passed following surgical shock showing microaggregates* (**a**) (*original magnification* × *40*). *Transmission electron micrography* (*original magnification* × *10 000*) *shows the aggregate core to be composed of highly activated and degranulated platelets* (**b**). *Before shock, scanning electron micrographs of screen filters through which vena caval blood had past showed little evidence of microaggregates*

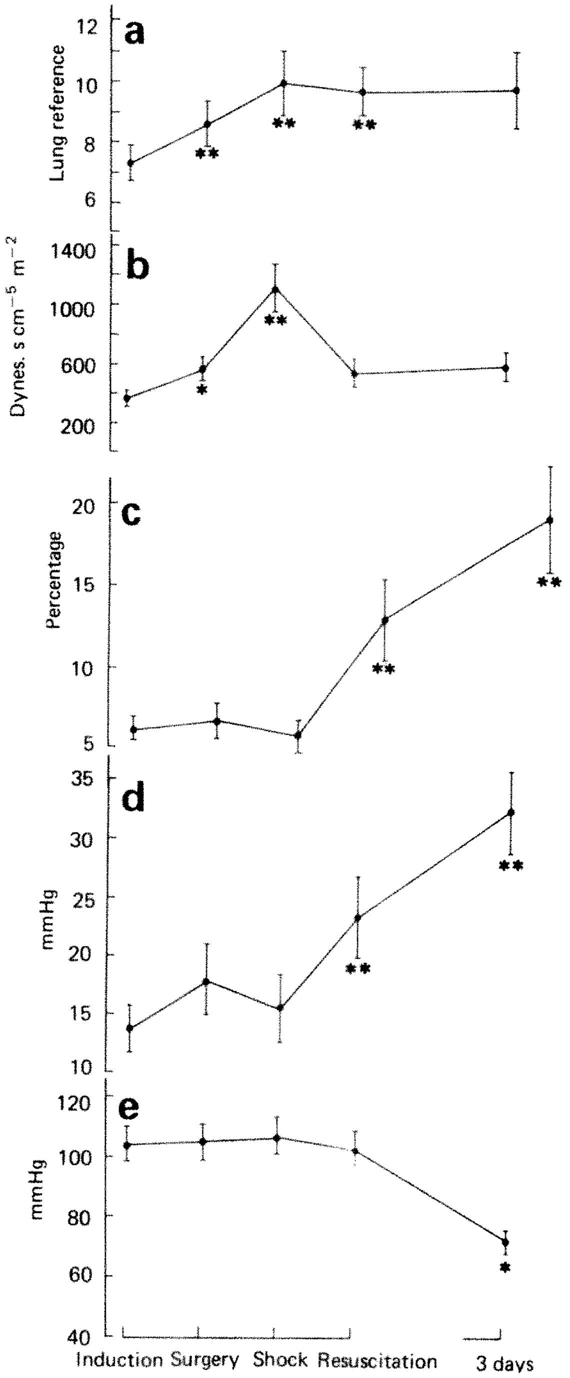

Figure 5 *Radiolabelled platelets accumulate in the lung during surgery and shock* (**a**) *with an associated increase in pulmonary vascular resistance index* (**b**). *Pulmonary shunt rises* (**c**) *following resuscitation, with resultant increases in lung dysfunction as demonstrated by alveolar–arterial oxygen difference* (**d**) *and a reduction in arterial oxygen tension* (**e**). *Values are mean ± s.e.m.* $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}01$

Falls in platelet and leucocyte counts are well described in many shock states and are known to be associated with acute respiratory failure[14–16]. The explanation may be the formation of platelet and leucocyte aggregates in peripheral blood[12]. The results of screen filtration pressure measurements in our study demonstrate that aggregates appeared in vena caval blood at the same time as the fall in platelet and leucocyte counts were first detected. On electron microscopy, these aggregates consisted almost entirely of platelets with no significant leucocyte involvement. The fall in circulating leucocyte numbers probably results from leucocyte margination in the lung, possibly initiated by endothelial injury following platelet microembolization or by release of thromboxanes which are known to produce leucocyte adhesion to endothelium[17].

Although the importance of microembolization in pulmonary dysfunction following shock remains uncertain, it is now accepted that this microembolization does occur[13,18,19]. The increase in pulmonary radioactivity in our model confirms the accumulation of platelets which has previously been demonstrated by platelet sequestration studies in endotoxic and traumatic shock[20,21]. The subsequent development of severe pulmonary arteriovenous shunting in our pigs was similar to changes reported following elective aneurysm surgery in patients when shunting more than doubled in the early postoperative period and was associated with pulmonary platelet sequestration[11]. In our model, platelet and leucocyte counts continued to fall postoperatively and, despite the death of those pigs which presumably had the worst pulmonary damage, pulmonary function in survivors deteriorated yet further by 3 days. These changes may have resulted from further sequestration of platelets and leucocytes in the pulmonary microvasculature or from the release of vasoactive substances including thromboxanes, leukotrienes and oxygen free radicals which promote further pulmonary damage[22–24].

Although the relationship between vena caval aggregates, pulmonary platelet uptake, the development of pulmonary shunting and subsequent impaired oxygenation of arterial blood was impressive, proof that the aggregates cause pulmonary damage still depends on demonstrating that prevention of aggregates will also improve pulmonary function following surgery or severe shock. The prevention of such aggregates is conceivable in modern surgery and may possibly be achieved by prostaglandin therapy or by removing the relevant blood cells before surgery and returning them to achieve haemostasis when the operation is completed.

Acknowledgements

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Short note

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Suction drainage of the axilla: a prospective randomized trial

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Suction drainage of axillary wounds after surgery for breast cancer is widely employed to prevent the development of postoperative seromas. Such drains could offer a portal to infection and may even encourage continued drainage either because of the suction applied or an irritant effect. Drainage has not been previously shown to reduce seroma formation and the omission of a drain might shorten hospital stay, reduce demands on nurses, and lessen postoperative discomfort. We have conducted a prospective randomized clinical trial to determine their value.

Patients and methods

At operation the ipsilateral axilla was approached through a separate incision from that used to remove the primary tumour. Contents of the axilla were cleared below the axillary vein by a standardized technique[1] The breast wound was not routinely drained. After haemostasis had been achieved the diathermy was replaced in its sheath and the patient randomized using a sequentially numbered sealed envelope. Where allocated, a single closed suction drain (Redivac®, Biomet Ltd., Bridgend, UK) was inserted into the axilla Further use of the diathermy was prohibited.

After the operation the wound was examined daily for the development of a seroma until discharge from hospital. Drains were removed when considered to have ceased functioning, i.e when under 25 ml of fluid had been drained in the previous 24 h. Patients have generally received uniform advice on shoulder exercise from a trained nurse counsellor[2]

After discharge from hospital, follow-up and treatment were not uniform, therefore data have not been collected concerning the subsequent incidence of late complications.

Table 1 *Comparison of patients who underwent suction drainage and those who did not undergo drainage after axillary surgery*

	No drainage	Drainage	Significance
Number of patients	20	20	
Mean age in years (±s e.m.)	50 (±2·6)	52 (±2·7)	n.s.†
Perioperative tamoxifen	13	13	n.s *
Postoperative seroma	9	2	$P<0{\cdot}04$*
Mean postoperative stay in days (±s e.m)	3·4 (±0·3)	3·9 (±0·3)	n s †

* χ^2 test, Yates' continuity correction, 1 d f , † Student's *t* test

Results

Forty consecutive patients undergoing axillary clearance as part of primary surgical treatment for carcinoma of the breast were entered into this trial. Twenty patients were allocated a suction drain. The two groups had similar demographic factors (*Table 1*). No patient suffered a wound infection.

After surgery nine seromas developed in the twenty patients who did not have a drain inserted. Two seromas occurred in the drainage group ($P<0{\cdot}04$, χ^2 test). Duration of hospital stay was slightly increased in the group who were drained but this did not reach statistical significance.

Discussion

Troublesome collections of fluid are common following surgery for breast disease[3] These seromas may occur either beneath the skin flaps produced by a mastectomy scar or within the axilla. The changing management of early breast cancer has brought about the wider implementation of conservative surgery This utilizes lumpectomy and additionally the axillary contents are commonly cleared to provide valuable prognostic information allowing a rational choice of adjuvant therapy. A previous study from this department found that tamoxifen, widely used as an adjuvant treatment for breast cancer, increased the incidence of axillary seromas[4]. To prevent the development of seromas suction drains are inserted in the axilla, but the continued loss of serous fluid may delay discharge from hospital. In other areas of the body suction drains have been found to increase the incidence of fluid collections[5].

The results of our study confirm the high incidence of seroma development following axillary clearance. Unless suction drains are employed we consider that the incidence is unacceptably high. Drainage does not rule out the possibility of seroma development and has disadvantages in terms of expense, nursing time and possible prolongation of hospital stay. We are therefore currently investigating further therapeutic manoeuvres in an attempt to solve this problem.

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Effect of transdermal glyceryl trinitrate on the survival of peripheral intravenous infusions: a double-blind prospective clinical study

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Phlebitis is the commonest complication of intravenous infusion. It has been suggested that it is initiated by venoconstriction at the infusion site, hence treatment with a vasodilator may reduce its incidence. We carried out a prospective double-blind controlled study of the effect of transdermal glyceryl trinitrate on the survival of peripheral intravenous infusions in 340 patients. Fifty-five per cent (94 out of 170) of the infusions failed in the control group compared with 19 per cent (33 out of 170) in the treatment group ($\chi^2 = 45$, $P < 0.0005$). The commonest cause of infusion failure was superficial phlebitis: 47 per cent in the control group and 17 per cent in the treatment group ($\chi^2 = 46$, $P < 0.0005$). The estimated median time of infusion survival was 74 h in the control group compared with 127 h in the treatment group (log rank $\chi^2 = 143$, $P < 0.0001$). We conclude that infusion phlebitis is a common problem in hospitalized patients and its incidence can be effectively reduced by transdermal glyceryl trinitrate.

Keywords: Intravenous infusions, phlebitis, glyceryl trinitrate

Infusion phlebitis is a common cause of morbidity in hospital practice. It is the commonest complication of intravenous therapy and its reported incidence varies between 30 and 70 per cent of infusions[1–5]. Many factors contribute to its development which makes prevention difficult. In most cases such prevention saves the patient from a minor but rather painful condition; but when few peripheral veins are available it becomes very important to prolong the life of each infusion site.

It has been suggested that infusion phlebitis and extravasation are initiated by venoconstriction at the infusion site brought about by irritation of the endothelium[6] and, therefore, it may be possible to reduce their incidence by keeping the infused veins dilated. Wright *et al.*[7] have reported that transdermal glyceryl trinitrate (GTN) patches applied close to the cannulation site reduced the failure rate of peripheral intravenous infusions. This could be invaluable in the prevention of phlebitis and extravasation, thereby saving patients considerable discomfort and worry and decreasing the workload for hospital staff. However, a criticism of the study design of Wright *et al.*[7] is that their patients came from different wards within a hospital where techniques of cannulae siting, the size and nature of the cannulae used and the care of intravenous infusions may be different. They replaced the GTN patch after 3–4 days on the assumption that the release of the drug is constant over that period. The manufacturer's data sheet does not give release rates for periods exceeding 24 h and Riess *et al.*[8] have reported that the GTN plasma concentration falls if the same patch is worn for longer than 48 h. Therefore, we studied the effect of GTN patches on the survival of peripheral intravenous infusions in a controlled population where the patches were changed daily.

Patients and methods

This prospective double-blind controlled trial took place on a general surgical unit with 62 beds. All patients between 16 and 80 years of age and requiring intravenous therapy were considered Hypovolaemic and seriously ill patients, those with glaucoma and/or an unstable cardiovascular system, those on anti-inflammatory or vasodilator drugs, those receiving blood transfusion, and those who were known to be allergic to GTN or Elastoplast® (Smith and Nephew Ltd., UK) were not entered in the study The protocol was approved by the local ethical committee and all patients gave written informed consent

A total of 340 patients entered the trial and were randomized to receive, immediately after the venous cannulation, a self-adhesive patch of either Transiderm-Nitro 5® (Ciba-Geigy Pharmaceuticals, Horsham, UK; Transderm Nitro 5® in the USA) which releases 5 mg GTN daily at a continuous rate, or identical placebo systems. The patches were contained in coded boxes, one box being randomly allocated to each patient. The randomization was carried out independently and was stratified to avoid a between-group discrepancy in the male.female ratio The key to randomization was held by the principal pharmacist and released at the end of the study for data analysis. The patches were applied distal and as close as possible to the cannulation site and replaced daily For those cannulae sited on the dorsum of the hand, the patches were placed alongside the cannulae

The same make of infusion sets (Continu-Flo®, Travenol Laboratories Ltd , Egham, UK) and TEFLON* cannulae (Venflon® 2, Viggo, Helsingborg, Sweden) were inserted by a team of four doctors (junior surgeons) according to standard procedures for preparing and caring for the intravenous sites and for inserting the cannulae. The site of insertion was prepared using a cleansing wipe saturated with 70 per cent v/v isopropyl alcohol BP (Sterets® Alcowipe, Seton-Prebbles Ltd.) The same dressing (Vecafix®, Viggo, Swindon, UK) was used to cover all cannulae. If a haematoma developed at the puncture site or if access to a vein was not achieved after two puncture attempts, a new site was chosen (preferably in the other limb) Only the upper limbs were used The ease of siting the cannulae was graded for each patient on the following subjective scale: very easy, easy, difficult, very difficult All patients were given a mobility score: zero for patients who were bedridden for more than 50 per cent of the time, and one or two for patients who were, respectively, partially or fully mobile for more than 50 per cent of the time All additives were introduced by doctors or trained nurses using standard aseptic techniques

The infusion was discontinued and the cannula removed when it was no longer required for treatment or when it failed Failure of infusion was defined as the occurrence of either phlebitis or extra-

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Table 1 *Comparability of groups*

	Control ($n = 170$)	Treatment ($n = 170$)
Mean age (years)	52·5	51·5
Male:female	70:100	70:100
Cannula size		
14 G	11	12
16 G	109	99
17 G	1	0
18 G	46	59
NA	3	0
Cannula site		
Dominant non-dominant limb	53.117	54:116
Dorsum of hand	23	23
Wrist	20	22
Forearm	122	120
Cubital fossa	4	5
NA	1	0
Intravenous additives		
Antibiotics	12	25
Potassium chloride	10	14
General anaesthetic	2	0
None	137	123
NA	9	8
Ease of siting of cannula		
Very easy	52	44
Easy	104	98
Difficult	7	22
Very difficult	0	1
Sited under general anaesthetic	2	0
NA	5	5
Mobility score		
0	50	43
1	113	109
2	4	9
NA	3	9

NA, information not available

vasation and/or an irregular infusion rate. Phlebitis was defined as the presence of two or more of the following signs: pain, erythema, swelling, excessive warmth, and/or palpable venous cord Only one infusion site was studied per patient

Venepuncture sites were inspected by the same investigator, together with a trained nurse, 12-hourly or when an irregularity of infusion rate or the patient's discomfort was reported Information including age, sex, patch number, date, time, site and ease of cannulation, size of cannula, nature of the infusate and additives, mobility of patient, evidence of irregularity of infusion rate, signs of phlebitis and extravasation, and times of removal of cannula were recorded on a standard form for each patient.

Failure incidence was analysed by life-table methods, the log rank test and proportional hazard modelling using the computer package BDMP[9,10]. These methods take into account not only differences in cannulae survival but also the fact that since many cannulae are removed for reasons other than failure (censored observations), the number of surviving cannulae that can fail decreases with time

Results

The mean age of the 170 patients in the treatment group was 51·5 years (range 16–80) compared with 52·5 years (range 16–79) for the 170 patients in the control group. The two groups were similar in terms of cannulae site and size, ease of siting of cannulae and mobility score of patients (*Table 1*). The intravenous fluids used were 4 per cent dextrose saline, 5 per cent dextrose in water, normal saline and Hartmann's solution, with the distribution being equal between the control and treatment groups. Antibiotics and potassium chloride were the most common additives infused. Twenty-five patients received antibiotics in the treatment group compared with twelve in the control group, whereas the frequency of use of potassium chloride was similar in both groups (*Table 1*). The non-dominant limb was used more often than the dominant (117 (69 per cent) control, 116 (68 per cent) treatment) with the forearm being the commonest site of cannulation (122 (72 per cent) control, 120 (71 per cent) treatment).

There were 94 (55 per cent) failed infusions in the control group compared with 33 (19 per cent) in the treatment group ($\chi^2 = 45$, $P < 0{\cdot}0005$). In all, 74 (43 per cent) cannulae survived the full length of treatment in the control group compared with 135 (79 per cent) in the treatment group ($\chi^2 = 40$, $P < 0{\cdot}0005$). The commonest cause of infusion failure was superficial phlebitis: 80 (47 per cent) in the control group and 29 (17 per cent) in the treatment group (*Table 2*, $\chi^2 = 46$, $P = 0{\cdot}0005$).

The estimated median time of cannulation was 74 h in the control group compared with 127 h in the group that received Transiderm-Nitro 5 (*Figure 1*; log rank $\chi^2 = 143$, $P < 0{\cdot}0001$). Differences in infusion survival between control and treatment groups remained significant when allowance was made for differences between the four doctors who inserted the cannulae, sex of the patient, cannulae size and site, mobility score, and drug additives using a proportional hazards model ($z = 10{\cdot}4$, $P < 0{\cdot}001$, relative risk of failure in the treatment group $= 0{\cdot}09$, 95 per cent confidence limits 0·06–0·15). Size 16 G and 18 G cannulae survived longer than size 14 G, irrespective of the treatment group (*Table 3*; relative risk of failure for 16 G cannulae = 0·51, 95 per cent confidence limits 0·26–0·98, and for 18 G cannulae = 0·39, 95 per cent confidence limits 0·19–0·78)

Headache and skin rash were the only side-effects noted and there was no between-group difference (*Table 4*).

Discussion

The aetiology of infusion phlebitis is multifactorial: duration[11–15] and site of infusion[11,14,16], rate of flow[11,17], nature of infusate and drug additives including the pH and particulate matter[5,12,13,17–22], size of vein[14,23], cannula size[23–25] and material[12,25,26], trauma at venepuncture[14,27], and infection[28,29] have all been incriminated. Of these, bacterial infection remains the most potentially serious problem as it could lead to suppurative phlebitis and septicaemia[30]. Several regimens have been suggested for prophylaxis including in-line filtration[5,31,32], neutralization of acid solutions[14,17] and the addition of steroids and/or heparin to the infusate[33–36]. However, filters are expensive and are used primarily for solutions with high particulate loads, such as antibiotics. Glucose solutions cannot be manufactured at neutral pH and their routine neutralization before use is not generally feasible. Heparin carries a small risk of bleeding in surgical patients and may (rarely) cause thrombocytopenia. Steroids may inhibit local defence mechanisms which could increase the risk of infective phlebitis. In view of the above, many clinicians have adopted the policy of frequently changing the infusion site in an attempt to reduce the incidence of phlebitis.

In clinical practice, concentrated solutions and irritant drugs are given via central rather than peripheral veins because the greater blood flow in central veins rapidly dilutes the infusate and removes the irritant. Therefore, the concept of increasing

Table 2 *Reasons for removal of cannulae*

	Control	Treatment
End of treatment	74 (43·5)	135 (79·4)
Phlebitis	80 (47·1)	29 (17·2)
Extravasation	1 (0·6)	1 (0·6)
Irregular infusion rate	0	1 (0·6)
More than one reason*	13 (7·6)	2 (1·2)
Patients opted out of trial	2 (1·2)	2 (1·2)

*A combination of the following: thrombophlebitis, extravasation, irregular infusion rate Values in parentheses are percentages

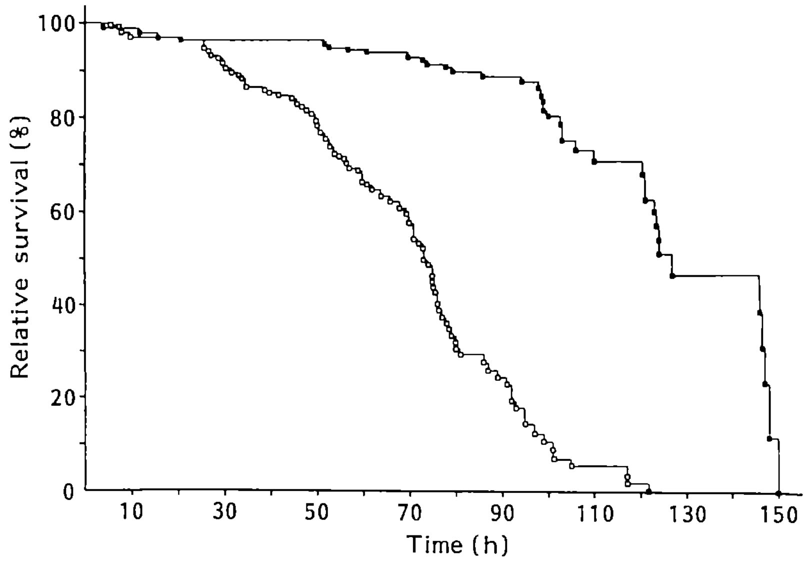

Figure 1 *Relative survival of infusions in the treatment and control groups. Each point represents the time when one or more infusions were discontinued for failure or end of treatment.* ■, *Treatment,* □, *control*

Table 3 *Cannulae size and infusion survival (hours)*

	Control			Treatment		
	Mean time (h)	s.e.m	*n*	Mean time (h)	s.e.m	*n*
14 G	57·8	9·8	10	87·7	11·2	12
16 G	69·7	2·8	108	119	4·6	97
17 G	65	—	1	—	—	—
18 G	75·1	4·0	46	130	4·8	59
NA	—	—	5	—	—	2

NA, information not available

Table 4 *Adverse reactions*

Reaction	Control	Treatment
None	160	156
Headache, trial stopped*	6	6
Headache, trial continued†	2	5
Skin rash, trial stopped‡	2	3

* Patients opted out of trial; † headache responded to analgesia and patients opted to carry on with trial; ‡ trial stopped on suspicion of an allergic reaction

the blood flow in peripheral veins is appealing and may reduce the incidence of infusion phlebitis. Transdermal GTN has been shown to induce local vasodilatation[37,38], and sublingual GTN has been reported to increase blood flow while decreasing vascular resistance and venous tone in the forearm[39]. Transiderm-Nitro 5 releases 5 mg GTN daily at a constant rate. If the aetiology of phlebitis is infective then venodilatation induced by GTN could reduce the incidence by allowing neutrophils easy access to the contaminated site.

Our results are in agreement with those of Wright *et al.*[7] and confirm the beneficial effects of Transiderm-Nitro 5 patches in reducing the incidence of peripheral intravenous failure. At first, it would appear that changing the GTN patch daily has no significant advantage over the cheaper and simpler strategy of changing it every third or fourth day. However, comparing the infusion survival curves of Wright *et al.*[7] with ours reveals that while the placebo survival rates are very similar, the treatment survival rates are different. The relative survival in the treatment group at 96 h is better in our study (0·91) where the patch is changed daily than in the study of Wright *et al.*[7] (0·70) where the GTN patch is changed every third or fourth day. This marked difference is unlikely to be affected by the inevitable minor inaccuracies due to interpolating survival probabilities for the study of Wright *et al.* from their published survival curve[7]. Further studies evaluating dose regimens are needed to find the adequate dose required to obtain optimal effect.

The effect of GTN may not be due solely to local vasodilatation. The drug has been shown to stimulate synthesis of prostacyclin by cultured human endothelial cells[40]. Prostacyclin is a potent inhibitor of platelet aggregation and is synthesized in vascular walls by prostaglandin endoperoxides[41]. It has been suggested that, following vascular injury, endothelial damage could reduce prostacyclin synthesis, resulting in regional vasoconstriction[42]. The potent vasoconstrictor thromboxane A_2 is then produced by aggregating platelets in the damaged area. Prostacyclin, which also relaxes smooth muscle cells in vein walls, may be produced in increased amounts by surrounding undamaged endothelial cells The maintenance of an effective concentration of prostacyclin at infusion sites in veins (by the use of GTN) may help to relax smooth muscle and prevent venoconstriction and platelet aggregation, thereby possibly reducing the incidence of infusion thrombophlebitis.

The populations in the treatment and control groups were similar, except that more cannulae in the treatment group were difficult to site (22 treatment, 7 control) and more infusions received antibiotic additives (25 treatment, 12 control). Nevertheless, despite this possible deleterious bias within the random selection, the incidence of infusion failure was significantly lower in the treatment group (33 infusions) than in the control group (94 infusions)

The incidence of headaches and skin rashes was similar in the control and treatment groups. The skin rash is more likely to be due to the adhesive part of the patch and not to the GTN. The incidence of headache in surgical patients has not been reported and it may be greater than in the normal population. However, the incidence of headache in the treatment group (6 per cent) was lower than in that reported by Wright *et al.*[7] (14 per cent) in a similar study.

The incidence of phlebitis in the control group (47 per cent) is similar to that reported by Dinley[12], Emerin and Marshall[14] and Collin *et al.*[28]. The finding that smaller size cannulae survived longer than larger ones irrespective of the treatment group is in agreement with the findings of Swanson and

Aldrete[23] and those of Curry and Zallen[24] Thrombus formation is related to the size of the cannula[25,43]. Therefore, a build-up of thrombus on a small cannula may be less likely to occlude the vessel. Even a partial occlusion may impede blood flow and produce a deleterious effect on the endothelium by the undiluted infusate[25]

Apart from the important benefit of improved patient's welfare, the central issue is one of cost-effectiveness. The cost sequelae of infusion failure are those of staff time and material costs of re-infusion. The differential failure rate between the treatment and control groups is so marked (*Figure 1*) that it is likely to offset the initial cost of the daily change of the transdermal GTN patch. Cost–benefit analyses are needed to examine the cost implications of this new treatment to reduce the incidence of peripheral intravenous infusion failure.

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Definitive one-stage emergency large bowel surgery

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During a 30-month period, 126 operations for emergency large bowel conditions were performed: 57 were for colonic carcinoma, 26 for acute diverticulitis, 14 for colonic ischaemia, 13 for complications of inflammatory bowel disease, and 16 for other conditions. Sixty-eight patients had peritonitis. One hundred and ten patients (87·3 per cent) underwent immediate resection. Of these, 83 (65·9 per cent of the overall group) had colonic resection with primary anastomosis but without a colostomy, 56 of which were left-sided colonic resections. Excluding 9 of the 68 patients with peritonitis, who had a total colectomy, 66 per cent also underwent resection, anastomosis and no colostomy. Total group mortality was 14·3 per cent: 12·7 per cent in the immediate resection group, 9·6 per cent in those with primary anastomosis and no colostomy, 5·2 per cent in the group with peritonitis undergoing resection and anastomosis, and 25 per cent in those having non-resectional surgery. Complications included an overall wound infection rate of 10·3 per cent and a clinical anastomotic leak rate of 7·2 per cent in those who had anastomosis without colostomy. Our results suggest that resection and primary anastomosis can be performed with acceptable morbidity and mortality in a high proportion of cases of emergency large bowel conditions, irrespective of underlying pathology, site of disease or the presence of peritonitis.

Keywords: Emergency, one-stage colon surgery

Despite advances in critical care, surgery for emergency large bowel conditions continues to be frequently associated with an unsatisfactory outcome. Traditionally, large bowel emergencies were treated in stages[1], but more recently there has been a trend towards definitive surgery with immediate resection, and anastomosis under certain conditions[2–5]. Peritonitis, however, is frequently regarded as a contra-indication to primary resection and immediate anastomosis, although there is some clinical and experimental evidence to refute this view[6–8].

Emergency large bowel conditions occur predominantly in the elderly. Initial management by performing a colostomy is often unsatisfactory. palliation is poor and colostomy management in the frail patient can be difficult. Additionally, many such stomas are never closed[9–12] In recent years our approach has been to avoid a colostomy except for compelling reasons. Our results, based on 126 consecutive cases, suggest that this approach is not associated with increased morbidity or mortality over traditional management and may be associated with better palliation and rehabilitation of the patient.

Patients and methods

Between January 1985 and June 1987, 126 emergency large bowel operations were performed in Worthing District Hospital The population served was 240 100, of whom 33 per cent were older than 60 years (1985 figures). The study was retrospective for the first 6 months and prospective thereafter. If a diagnosis of acute large bowel pathology was made at laparotomy, the subject was entered into the study and evaluated until discharge, death, or to the end of the study period.

Patient details collected included age, sex, pre-operative and total hospital stay, clinical and pathological diagnoses, cancer stage and degree of peritonitis if present, operation performed, surgeon, complications, mortality, presence of colostomy and details of colostomy management. Emergency surgery was defined as a colonic operation without preceding bowel preparation or arising from complications of large bowel investigation or preparation. Our current practice involves mechanical bowel preparation in all patients undergoing elective colorectal operations in this hospital A standard operative protocol was performed by consultants and registrars. Incisions were paramedian, wound drapes were never used, anastomoses were inverting and two-layered using 2/0 chromic and 2/0 silk, and corrugated drains were placed near all anastomoses. Peritoneal lavage using 2–3 litres of 0·9 per cent saline was performed for all cases of generalized peritonitis, no antibiotic was added to this solution On-table colonic lavage was not performed, if faecal loading was a problem the bowel was evacuated by manual compression into a bowl. This followed resection of the lesion and isolation of the distal clamped bowel outside the abdomen, thereby preventing faecal soiling.

Primary anastomoses were carried out if the operating surgeon felt that the local conditions such as blood supply, mesenteric tension and tissue friability were adequate The wound, including skin, was closed in layers. All patients received 1 g cefuroxime and 500 mg metronidazole intravenously perioperatively. Two further doses were always given. In the presence of sepsis or peritoneal soiling, antibiotics were continued for 7 days Wound sepsis was defined as any collection of wound pus, excluding stitch sinuses, before discharge Any faeculent discharge from the drain site was considered an anastomotic leak, no radiological studies were performed. Perioperative death was defined as mortality within 1 month of operation, or death in hospital before discharge Other major complications were based on accepted clinical and investigative criteria

Pathological staging of tumours was based on the Aster and Coller modification of Dukes' classification[13], with a 'D' classification indicating intra-abdominal metastases (*Table 1*) The degree of peritonitis was classified by the method of Hughes[14] as modified by Krukowski and Matheson[5] (*Table 2*)

All data were analysed on a microcomputer (Macintosh SE, Apple computers) using a standard database (Filemaker) and statistical package (Statview 512+) Results are expressed as mean ± s.e m. Student's t test, analysis of variance, and χ^2 tests with Yates' correction were used for comparing groups as indicated. Differences were considered significant when $P < 0{\cdot}05$.

Results

Over the 30-month study period, 126 patients were operated on for acute large bowel conditions. Of the total, 81 were women and 45 were men, with a mean age of 69·9 years (s.e.m ± 1·4,

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range 15–96 years). The ratio of women to men (1·7:1) is consistent with sex ratios in the Worthing district in this age group. Acute referrals accounted for ·122 cases; 2 patients presented with complications of colonoscopy and a further 2 cases, 1 obstruction and 1 perforation, arose following barium enema. Apart from the latter four cases, diagnoses were based on clinical examination with plain abdominal X-rays and were confirmed at laparotomy.

Table 1 *Site and histological classification of tumours in patients with olorectal carcinoma*

Site	Histological classification					Total
	B_1	B_2	C_1	C_2	'D'	
Caecum			15	2	2	19
Hepatic flexure					2	2
Transverse colon	1				1	2
Splenic flexure		2	3		1	6
Descending colon	1		1		2	4
Rectosigmoid	1	4	12	3	4	24
Total	3	6	31	5	12	57

Table 2 *Underlying aetiology and pathological grade of peritonitis*

Site	Pathological grade					Total
	A	B1	B2	C1	C2	
Carcinoma		4	1	7	1	13
Diverticulitis	8	7	4	4	3	26
IBD						
Crohn's	4					4
Colitis	4			4		8
Ischaemia	2			3	1	6
Miscellaneous	2	5	1	3		11
Total	20	16	6	21	5	68

Classification: A, acute inflammation without free pus, B1, localized abscess; B2, localized peritonitis; C1, generalized purulent peritonitis; C2, generalized faeculent peritonitis, IBD, inflammatory bowel disease

The pathological and clinical diagnoses and the operative procedures performed are listed in *Table 3*; 110 patients (87·3 per cent) underwent immediate resection; 88 (69·8 per cent) had resection and primary anastomosis, of whom 5 had a colostomy because of particular peroperative concern regarding the anastomosis. Of the 83 who had resection, anastomosis and no colostomy, 32 underwent right-sided and 51 left-sided resections As expected, a higher proportion of patients with right-sided obstruction and peritonitis underwent resection and primary anastomosis (88 per cent and 90·9 per cent respectively) than those with left-sided disease (80·6 per cent and 60·4 per cent).

The total peritonitis group is shown in *Table 2*. Twenty-six patients had generalized peritonitis (grades C1 and C2); of these, sixteen had resection and anastomosis (two had a colostomy and two were right-sided lesions). Four of the ten remaining patients with peritonitis had some form of total colectomy, four had Hartmann's procedures, and two had a defunctioning colostomy only.

Diagnostic and operative group mortality figures and details of the deaths that occurred are shown in *Tables 4* and *5*. The highest group mortality was in those with inflammatory bowel disease. The four deaths in this group occurred in those with acute colitis (44 per cent), three of whom underwent proctocolectomy while the fourth patient had a total colectomy and ileostomy. There was a trend towards a higher mortality rate in patients undergoing conservative or non-resectional surgery (25 per cent), than in those undergoing immediate resection (12·7 per cent), or primary anastomosis and no colostomy (9·6 per cent), although this did not reach statistical significance ($\chi^2 = 1{\cdot}98$, n.s.).

There was no age difference between survivors and non-survivors ($69{\cdot}9 \pm 2{\cdot}6$ *versus* $71{\cdot}2 \pm 2{\cdot}9$; analysis of variance, Dunnett t test = 1·609, n.s.). The major complications seen are listed in *Table 6*. One or more complications occurred in 58 patients, 14 patients had 2 or more, and 11 of the 18 deaths occurred in this latter group ($\chi^2 = 11{\cdot}7$, $P > 0{\cdot}01$). Eight patients developed multiple organ failure, all of whom died. Seven anastomotic leaks occurred, six in patients with no colostomy; this group contained three each from right- and left-sided resections. Two of the left-sided leaks were converted to end colostomies, and the remaining five settled without further surgical management. None of these patients died. Three

Table 3 *Operations performed in the different aetiological and clinical groups*

	Resection + anastomosis	Hartmann's	Bypass only	Colostomy only	Drain only	Total colectomy	Total
Diagnosis							
Carcinoma	43 (2)	7	3	4			57
Diverticulitis	16 (1)	4		4	2		26
IBD							
Crohn's	4						4
Colitis						9	9
Ischaemia	12 (1)	2					14
Miscellaneous	13 (1)				3		16
Total	88	13	3	8	5	9	126
Site							
Left colon							
Obstruction	25 (3)	5		1			31
Peritonitis	29 (2)	8		7	4		48
Haemorrhage	2						2
Right colon							
Obstruction	22		3				25
Peritonitis	10				1		11
Total colon							
Colitis						9	9
Total	88	13	3	8	5	9	126

Numbers in parentheses indicate patients who also received a colostomy, IBD, inflammatory bowel disease further faecal fistulae occurred in non-anastomotic cases, all of which resolved spontaneously.

Surgeons of registrar status performed 104 of the 126 operations (82·5 per cent). Within this group, a total of 14 deaths and 32 complications occurred, while 4 deaths and 33 complications occurred in the non-registrar group. Frequency of deaths and complications were similar in both groups ($\chi^2 = 0{\cdot}078$ and 0·5 respectively, n.s.) Also, the complication rate in patients following resection anastomosis and no colostomy was no greater (32 complications in 83 patients) than in those who had a closable stoma (15 complications in 28 patients, $\chi^2 = 1{\cdot}22$, n.s.)

Following primary operation, 91 patients (72·2 per cent) had no colostomy. Three patients had colostomies fashioned at a second operation; two for anastomotic leaks and one patient had a loop colostomy following the placement of a drain for severe acute diverticulitis. Nine patients had total colectomies or proctocolectomies. Thus there were 29 patients with a stoma for closure. Of these, 12 (41·4 per cent) had their stoma closed at the completion of the study; of the remaining 17 with colostomies, 5 had died and 10 were considered unfit for further surgery by the end of the study period.

The mean duration of in-hospital stay was 20 ± 1·2 days (range 2–154 days). The in-hospital duration of the group with colitis was 42·8 ± 8·7 days (range 19–105 days) which was significantly greater than all other groups as was their preoperative in-hospital duration of 11·9 ± 3·2 days *versus* 2·78 ± 0·4 days (unpaired t test, $P < 0{\cdot}05$). The initial duration of in-hospital stay of the colostomy group was 22·9 ± 2·3 days while that of the resection, anastomosis and no colostomy group was 19 ± 1·3 days (analysis of variance, Dunnett t test = 0·651, n.s.). For those whose colostomies were closed, the mean total in-hospital stay was significantly longer than that of the group without colostomies (analysis of variance, Dunnett t test = 21·16, $P < 0{\cdot}001$).

Table 4 *Mortality recorded by aetiological and operative groups*

	Number	Percentage of each diagnostic or operative group
Diagnostic group		
Carcinoma	5	8·8
Diverticulitis	4	15·4
Colitis	4	44·4
Ischaemia	3	21·4
Miscellaneous	2	12·5
Total	18	14·3
Peritonitis	10	14·7
Operative group		
Resection + anastomosis	8	9·6
Hartmann's	2	15·4
Total colectomy	4	44·4
Non-resectional surgery	4	25
Total	18	14·3
All resections	14	12·7

Discussion

The trend towards definitive surgery for emergency large bowel conditions stems from the realization that, in the elderly, mortality following staged procedures may be greater than for definitive surgery carried out at initial presentation. Moreover, many such patients die or are too frail to complete their protracted surgical treatment[3,10]. Further practical benefits of a definitive approach include the establishment of a firm diagnosis, elimination of the pathological lesion, and better control of sepsis by a more thorough laparotomy. Likewise, the cardiovascular, pulmonary and venous complications associated with multiple operations may be diminished. Important economic benefits should also result from the significantly decreased in-hospital duration demonstrated using this approach[3].

Theoretical benefits of this approach include the improved

Table 6 *Types and frequency of complications seen in 58 patients*

Complication	Number	%
Wound infection	13	10·3
Pneumonia	8	6·3
Multiple organ failure	8	6·3
Anastomotic leak	7	8·0
Deep vein thrombosis	4	3·2
Stroke	4	3·2
Congestive cardiac failure	4	3·2
Myocardial infarction	4	3·2
Urinary retention (requiring TURP)	3	2·4
Confusion	3	2·4
Small bowel fistula	3	2·4
Pulmonary embolus	2	1·6
Acute renal failure	2	1·6

TURP, transurethral resection of the prostate

Table 5 *Details of patients who died*

Patient	Sex	Age	Diagnosis	Operation	Cause of death
1	M	86	Carcinoma	Resection + A	CCF
2	M	86	Carcinoma	Resection + A	Pneumonia
3	F	83	Carcinoma	Resection + A	CVA
4	F	69	Carcinoma	Hartmann's	Myocardial infarction
5	M	68	Carcinoma	Bypass	Pneumonia
6	F	83	Diverticulitis	Colostomy	Myocardial infarction
7	F	62	Diverticulitis	Colostomy	Persistent sepsis
8	F	49	Diverticulitis	Resection + A	MOF
9	F	65	Diverticulitis	Drain	Renal failure
10	F	54	U. colitis	Proctocolectomy	MOF
11	M	63	U colitis	Proctocolectomy	MOF
12	F	71	U colitis	Proctocolectomy	MOF
13	F	58	Colitis	Total colectomy	MOF
14	M	88	Ischaemia	Resection + A	Cardiac ischaemia
15	M	82	Volvulus	Resection + A	MOF
16	F	64	Ischaemia	Hartmann's	Stroke/pulmonary embolus
17	F	59	Lymphoma	Resection + A	MOF
18	F	76	Leiomyosarcoma	Resection + A	MOF

CCF, congestive cardiac failure, CVA, cerebrovascular accident, Resection + A, resection and anastomosis, MOF, multiple organ failure; U. colitis, ulcerative colitis ardiovascular status following resection of hyperemic bowel[15] Also, in patients with cancer, earlier resection of the neoplasm may have prognostic significance[15,16]. Of further interest is the possible adverse psychological effect of a colostomy on patient self-esteem, which may be important in the frail and elderly who may have limited dexterity and independence.

The main criticism of resection and primary anastomosis is the increased risk of anastomotic dehiscence with a high associated mortality[17,18]. Traditional contra-indications to primary anastomosis are the presence of sepsis and a loaded colon, although their relative importance to anastomotic healing is becoming less clear. There is some evidence to suggest that sepsis as an independent factor has little effect on anastomotic healing[6–8], and recently the adverse prognostic significance of faecal loading has also been questioned[19,20]. It is probable that anastomotic dehiscence is influenced by multiple local, systemic and technical factors, and therefore correction of one adverse factor may limit the detrimental effects of other influences. In this manner, colonic decompression by the methods described in this study may minimize any adverse effects of sepsis. Our method of colonic evacuation appeared to be effective and could be performed quickly, which may be to patient advantage in the elderly and critically ill.

Of the 126 patients reported here, 87·3 per cent had immediate resection at initial operation, 69·8 per cent had resection and anastomosis, and 65·9 per cent had an anastomosis with no colostomy. We carried out primary anastomoses in the presence of peritonitis in 39 of 59 patients who had surgery with the potential for restoring bowel continuity Within this latter group, 14 patients with generalized peritonitis had left-sided colonic resections.

Mortality and morbidity in this series compares favourably with that in other studies[10,21,22]. In the group with resection and anastomosis mortality was less than in those having non-resectional surgery. Also the frequency of complications and the duration of hospital stay were less in the former group than in patients receiving a colostomy, suggesting that mobilization and rehabilitation were also improved by this approach. The infection rate in this study of 10·3 per cent was comparable with that of others[19,21,23]; likewise our anastomotic dehiscence of 8·0 per cent was low and did not result in mortality. Of the six cases which occurred in patients with no colostomy, three each occurred following left- and right-sided resections. Although right-sided colonic resections are often technically easier, the incidence of complications is frequently comparable with that of left-sided colonic surgery[6,15,17].

The highest group mortality in this study occurred in the group with acute colitis. In the past, emergency proctocolectomy has had a higher mortality than total colectomy and ileostomy[24]. Three of the four deaths in this group occurred in patients undergoing proctocolectomy, indicating that this is still a hazardous procedure and suggesting that total colectomy and ileostomy or a modified Hartmann's procedure may be safer[25]. Also, earlier consultation between physician and surgeon is important in minimizing both nutritional and septic complications and the associated progressive organ failure which were particular problems in these patients with complications of ulcerative colitis.

This study demonstrates no difference in morbidity and mortality in emergency large bowel surgery carried out by surgical registrars and their seniors. This is in contrast to Phillips *et al.*[3] who found a 24 per cent registrar mortality rate and a 13 per cent consultant mortality rate in emergency surgery for malignant large bowel obstruction. While noting the emphasis on lack of consultant cover in perioperative deaths in the recent Confidential Enquiry into Perioperative Deaths (CEPOD) report[26], this study demonstrates what can be achieved by surgical registrars with experience who work closely with their senior colleagues.

The classical concept of avoiding colonic anastomoses in the presence of peritonitis or a loaded colon at all times is being increasingly challenged. Our results, which have important surgical, social and economic implications, further support this trend towards definitive one-stage emergency large bowel surgery. We conclude that for many elderly patients the absence of a colostomy after surgery for emergency large bowel conditions is feasible, safe, and will aid in mobilization and earlier discharge from hospital.

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Physiological changes after postanal repair and parameters predicting outcome

Nineteen patients have been studied before and 3 months after postanal repair. Physiological parameters have been compared with 16 age- and sex-matched controls. Twelve patients were substantially improved whereas seven obtained no clinical benefit. Pre-operative resting ($P<0.005$), squeeze ($P<0.005$) and strain ($P<0.005$) anal pressures at 2 cm were significantly less than controls. Similarly, pressures during all three events at 4 cm were significantly less than controls (resting $P<0.05$, squeeze $P<0.005$, strain $P<0.025$). Median volume of first leak during saline infusion was significantly less than controls ($P<0.005$) as was the total tolerable volume ($P<0.005$). Videoproctographic parameters which differed significantly from controls included pelvic floor descent at rest ($P<0.005$), during contraction ($P<0.005$) and straining ($P<0.05$); resting and squeeze perineal descent ($P<0.005$); and anal canal length at rest and straining ($P<0.005$). Anorectal angles, rectal compliance, rectal sensation and emptying did not differ from controls. None of these parameters was improved by postanal repair. Patients not improved by operation could be detected pre-operatively by low resting ($P<0.05$), squeeze ($P<0.025$) and strain ($P<0.05$) anal pressure at 2 cm as well as by videoproctographic evidence of increased pelvic floor descent at rest ($P<0.01$), during contraction ($P<0.005$) and straining ($P<0.005$), excessive perineal descent at rest ($P<0.05$), during contraction ($P<0.05$) and during attempted defaecation ($P<0.05$) and a short anal canal at rest ($P<0.05$) and during straining ($P<0.025$).

Keywords: Postanal repair, faecal incontinence, anal canal pressure, proctogram

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Faecal incontinence is thought to be associated with a deficient anorectal angle due to a neuropathy to the pelvic floor muscles[1–4] as well as the external anal sphincter. The condition is commonly associated with prolonged or obstructed labour or with chronic straining at stool.

Postanal repair has been reported to restore continence to a high proportion of patients[5,6], but a recent long-term follow-up from this unit to assess the quality of continence indicates that only 34 per cent of patients become completely continent[7]. The rationale for the operation is to repair a deficient anorectal angle and to lengthen the anal canal. Some physiological studies indicate that anal canal length, resting anal pressure and squeeze pressure are significantly improved after postanal repair[8]. Proctograms indicate that the anorectal angle is reduced in patients successfully treated by postanal repair[9].

We have undertaken a prospective clinical and physiological study in 19 patients with faecal incontinence who had been treated by postanal repair, to determine if any parameters might help to identify patients who are not improved by the operation.

Patients and methods

Nineteen patients with faecal incontinence underwent postanal repair for a deficiency of the levator ani and puborectalis between May 1986 and April 1987 using the technique already described[6,10] Two patients were men and seventeen were women. The median age was 59 years (range 30–78 years) The aetiology of incontinence was obstetric owing to prolonged labour but no sphincter injury ($n=11$), neuropathic ($n=5$), or was associated with a rectal prolapse in a group of patients who had undergone previous successful rectopexy but where the incontinence had persisted ($n=3$). Clinical and physiological evaluation was carried out before operation in all 19 patients and was repeated 3 months after the operation in 16. Physiological studies were compared with 16 age- and sex-matched control patients who had no gastrointestinal disease (median age 62 years (range 37–73 years), 2 male patients). A thorough clinical assessment was undertaken by questionnaire and interview 6 months after operation and patients were assigned to two groups treatment successes and those who were not improved by operation

Anal, anorectal and sigmoid pressures were measured simultaneously at 2, 4 and 26 cm from the anal verge after digital examination with the patient in the seated position. The seated position was used because previous studies had indicated that this was more reliable for assessment of anal manometry in incontinent patients than the conventional left lateral position[11]. Manometry was performed using a water-perfused four-channel catheter with side openings connected to a pressure transducer (Letromed*) and multichannel recorder (Multi-Trace 4, Lectromed). The catheter was introduced into the sigmoid colon with the patient in the left lateral position. In five patients radiographs of the pelvis were taken to confirm the position and to identify the manometric features of a kinked catheter The catheter was fixed to the left buttock by tape. Pressures were measured at rest, during maximum pelvic floor contraction and attempted defaecation

Rectal compliance and the recto-anal inhibitory reflex were assessed using a rectal balloon mounted on the four-channel catheter and positioned in the rectal ampulla just above the levator ani. The balloon was also connected through the catheter to a pressure transducer and pen recorder. Balloon pressure responses to incremental 50 ml increases in intrarectal volume were measured over the range 0–400 ml of air. Rectal compliance was calculated by dividing the increase in balloon volume by the pressure inside the balloon Reduction of more than 10 per cent of the resting anal pressure was recorded as an intact recto-anal inhibitory reflex.

Rectal sensation was assessed using the same rectal balloon. Three

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This paper was presented at a meeting of the Association of Surgeons of Great Britain and Ireland which took place in Harrogate, UK on 13–15 April 1988

* *Letromed is manufactured by Ormed Ltd , UK*

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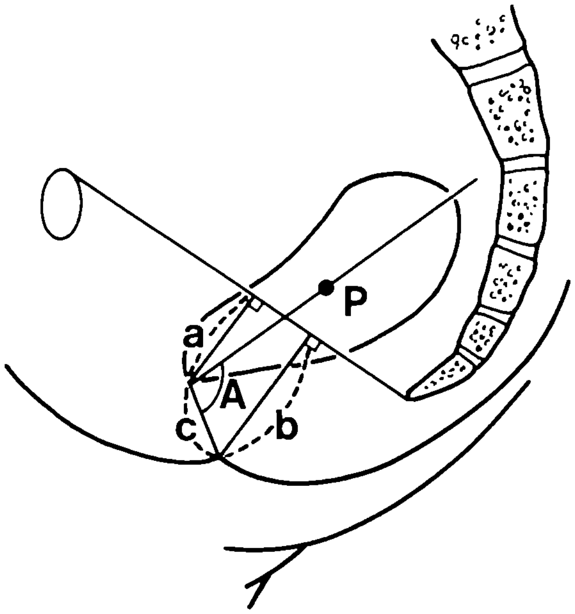

Figure 1 *Anatomical measurement in proctogram. A, anorectal angle, a, pelvic floor descent; b, perineal descent, c, anal canal length, P, centroid*

parameters of sensation were recorded according to the criteria of Farthing and Lennard-Jones[12]: threshold volume, volume associated with constant rectal sensation and volume below 400 ml at which pain became intolerable (maximum tolerable volume) Further volumes were not introduced for fear of bursting the balloon

A saline infusion test was used to test liquid continence A four-channel polyvinyl catheter (external diameter 5 mm) with side openings at 2, 4, 19 and 26 cm from the anal verge was inserted into the sigmoid. The catheter was connected to pressure transducers and a multichannel recorder so that the pressures at 2, 4 and 26 cm from the anal verge could be recorded while isotonic saline was being infused into the sigmoid through a 19 cm side hole in the catheter. The patient was seated on a special chair during the saline infusion test A total of 1500 ml isotonic saline (37°C) was infused at a rate of 50 ml/min by means of a peristaltic pump (H.R. Flow Inducer, Watson-Marlow Ltd., UK), and the subject was instructed to retain the saline for as long as possible without leakage. A commode was placed under the seat to collect any fluid that leaked from the anus. The volume infused at the time of the initial leak and the total volume retained at the completion of the infusion was recorded

The anorectal angle, pelvic floor descent, perineal descent and anal canal length were measured from radiographs taken during video-proctography. After marking the anal canal with Microtrast[*], 100ml (120 g) Baritop[†] mixed with cellulose to achieve a consistency similar to that of faeces was introduced into the rectum. The perianal skin and symphysis pubis were identified by surface markers The anorectal angle was measured between the longitudinal luminal axis of the anal canal and the longitudinal luminal axis of the rectum at rest, during maximum pelvic floor contraction and attempted defaecation. The longitudinal luminal axis of the rectum was obtained by drawing a line through the anorectal junction and the 'centroid' of the rectum The centroid was defined as the point which could divide a lateral projection of the rectum into two equal areas when a line was drawn from the centroid through the anorectal junction. The centroid was determined by a mathematical formula programmed to analyse lateral radiographs using a BBC microcomputer Pelvic floor descent was defined as the vertical distance between the pubococcygeal line and the anorectal junction. The vertical distance between the pubococcygeal line and the anal verge was used to measure perineal descent Anal canal length was defined as the distance between the anorectal junction and the anal verge (*Figure 1*). Measurements were carried out from lateral radiographs without magnification

Rectal emptying was also assessed during videoproctography by asking the patient to evacuate as much of the introduced contrast material as possible during 1 min The amount evacuated was weighed and the result was expressed as a percentage of the infused material

The Mann–Whitney *U* test was used for statistical analysis of the physiological data.

Table 1 *Quality of faecal continence*

	Total ($n = 19$)	Continence improved (treatment successes, $n = 12$)	Continence not improved (treatment failures, $n = 7$)
Median bowel frequency per day			
Pre-operative	3 (1–7)	3 (2–7)	2 (1–5)
Postoperative	1 (1–5)	1 (1–5)	3 (2–5)
Urgency			
Pre-operative	15	10	5
Postoperative	5	0	5
Soiling			
Pre-operative	16	10	6
Postoperative	9	3	6
Wearing pad			
Pre-operative	18	11	7
Postoperative	7	0	7
Failure of discrimination between flatus and faeces			
Pre-operative	13	6	7
Postoperative	10	3	7
True incontinence			
Solids			
Pre-operative	16	10	6
Postoperative	6	0	6
Liquids			
Pre-operative	19	12	7
Postoperative	8	1	7

Median and range values of bowel frequency are given

Results

Clinical

Of 19 patients having postanal repair, 12 patients stated that the quality of continence was considerably improved after the operation but 7 reported little if any clinical benefit. Median bowel frequency in patients who were improved decreased from 3 times (range 2–7) to once (range 1–5) per day but was not altered in those who had obtained no clinical benefit (*Table 1*) Urgency disappeared in all of the patients who were improved but persisted in all patients who were not. Soiling persisted in three of ten patients who were improved but was still present in six of six patients who had a poor result. None of the patients who were improved needed to wear a pad after operation, compared with all seven of those who were regarded as surgical failures. Failure of discrimination persisted in three of six patients who were improved but remained in all of the failures. Of the 16 patients who were incontinent of solids pre-operatively, 6 had persistent solid stool incontinence postoperatively; all were in the treatment failure group. Only 1 of 12 patients who were improved complained of liquid incontinence after operation, whereas incontinence to liquid persisted in all of those patients who obtained no clinical benefit.

Physiological

Anal canal pressures 2 cm from the anal verge were significantly lower before operation compared with controls at rest, during maximum pelvic floor contraction and attempted defaecation (*Figure 2*). However, there was no significant improvement in the parameters after operation in each position. Pre-operative anal pressures at 2 cm at rest, during pelvic floor contraction and attempted defaecation were significantly higher in patients who were improved compared with those who remained incontinent (rest: 50 (36–123) *versus* 29 (10–112) cmH$_2$O, $P < 0{\cdot}05$; during pelvic floor contraction: 90 (39–139) *versus* 38 (20–133) cmH$_2$O, $P < 0{\cdot}025$; attempted defaecation 79 (27–116) *versus* 54 (14–126) cmH$_2$O, $P < 0{\cdot}05$). Hence pre-operative anal pressures were found to be capable of predicting outcome (*Table 2*; *Figure 3*). Pressures at 4 cm from the anal verge and

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[*] *Microtrast is manufactured by Nicholas Laboratories, Dublin, Eire*

[†] *Baritop is manufactured by Ormed Ltd., UK*

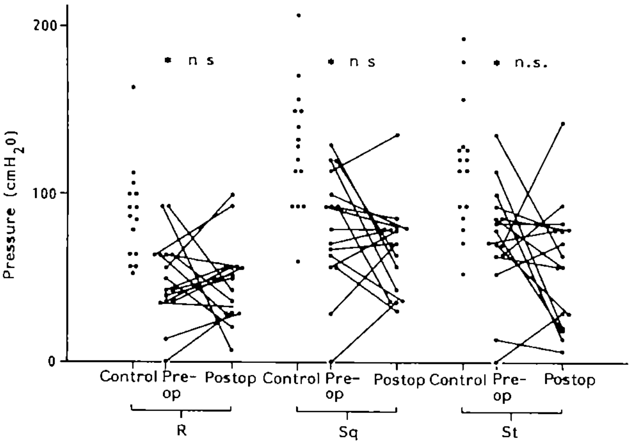

Figure 2 *Anal canal pressure (2 cm from the anal verge) before and after operation R, at rest; Sq, during pelvic floor contraction; St, during attempted defaecation, *P < 0·005 (pre-operative* versus *control group); n s., not significant (pre-operative* versus *postoperative)*

within the sigmoid colon did not change significantly after operation, although the pressures at both sites were significantly lower than controls before operation in all positions. Pressures at 4 and 26 cm did not predict outcome.

Parameters of rectal sensation did not differ from controls and did not change significantly after the operation. Median rectal compliance was 13·16 ml/cmH$_2$O (7·33–32·50) before operation compared with 14·50 (5·94–26·92) for controls and did not change significantly after operation, being 13·10 (6·00–19·16) irrespective of the outcome. Compliance did not predict outcome after postanal repair. The recto-anal inhibitory reflex was present in only 13 of 19 patients before operation compared with all the controls. In one patient the reflex was not restored after operation.

Volume at first leakage (VFL) during the saline infusion test and total tolerable volume (TTV) were significantly lower in patients than in the control group (first leak: 100 (40–600) ml *versus* 800 (80–1500), $P < 0·005$; total volume 150 (0–900) ml *versus* 900 (100–1500), $P < 0·005$). Retention of liquid improved in only one patient after operation (*Figure 4*). Neither VFL or TTV predicted outcome. Anal pressures 2 cm from the anal verge during the first 5 min of the saline infusion before operation were significantly lower than controls (maximal basal pressure, $P < 0·005$; minimum basal pressure, $P < 0·01$; peak pressure, $P < 0·005$) and significantly lower than those measured during the last 5 min of saline infusion (maximal basal pressure, $P < 0·01$; peak pressure, $P < 0·005$). However, no significant changes were observed after operation. Minimum pre-operative basal pressures during the last 5 min of the infusion were significantly greater ($P < 0·05$) in patients who were improved than in those who remained incontinent (*Table 2*). Hence anal manometry during saline infusion was capable of predicting outcome.

Pre-operative anorectal angles were not significantly more obtuse than those in the control group and there was no significant change in the anorectal angle after operation (*Figure 5*). Pre-operative assessment of anorectal angles did not predict the clinical outcome of operation. Median pre-operative values for pelvic floor descent compared with controls at rest were 5·0 (3·5–9·5) *versus* 3·6 (0·7–8·1) cm ($P < 0·005$); during maximum pelvic floor contraction these values were 4·7 (0·4–7·3) *versus* 2·4 (0·3–8·2) cm ($P < 0·005$); and during attempted defaecation these values were 7·1 (4·9–12·1) *versus* 5·3 (3·1–9·8) cm ($P < 0·05$). These parameters did not change significantly after operation (*Figure 6*) Pelvic floor descent predicted the outcome of operation during all three events (*Table 2*) Pre-operative perineal descent was also significantly longer than those measured in controls at rest. 7·3 (4·9–10·2) *versus* 8·0 (6·2–12·3) cm ($P < 0·05$) and during maximum pelvic floor contraction: 7·0 (3·9–10·2) *versus* 7·5 (5·7–10·7) cm ($P < 0·05$) before operation but did not change significantly after operation. Perineal descent measured pre-operatively also predicted the outcome of operation (*Figure 7*, *Table 2*). Anal canal length was significantly shorter than in the control group at rest: 3·6 (2·0–7·4) cm *versus* 2·5 (3·0–6·2), $P < 0·05$, and during maximum pelvic floor contraction: 3·9 (2·0–8·4) cm *versus* 5·6 (2·9–9·7), $P < 0·05$, but did not change significantly after operation. Pre-operative anal canal length at rest and during defaecation was significantly greater in those who were improved by the operation compared with those who were not (*Figure 7*, *Table 2*).

Median pre-operative rectal emptying was 75 per cent/min (range 0–100). This did not differ from controls or change significantly after operation.

Discussion

It used to be thought that patients with faecal incontinence had an obtuse anorectal angle due to a weak puborectalis sling and that postanal repair restored continence by reconstituting this angle[1,9,13]. In the past the anorectal angle has been defined as the angle between the luminal axis of the anal canal and a line drawn along the lower border of the distal rectum[14] or the longitudinal axis of the distal rectum[15]. The angle has been assessed by lateral projection videoproctography using various contrast materials such as a balloon filled with barium[9], barium-impregnated sponge[13] and barium mixed with

Table 2 *Positive predictive values*

	Improved ($n = 12$)	P	Not improved ($n = 7$)
Anal pressure at 2 cm (cmH$_2$O)			
R	50 (36–123)	<0·05	29 (10–112)
Sq	90 (39–139)	<0·025	38 (20–133)
St	79 (27–116)	<0·05	54 (14–126)
Pressure during saline infusion			
Minimum basal pressure (cmH$_2$O)			
Last 5 min	29 (7–57)	<0·05	7 (7–21)
Pelvic floor descent (cm)			
R	4·6 (3·6–7·4)	<0·01	7·6 (5·6–9·5)
Sq	4·0 (−0·4–7·0)	<0·005	6·4 (5·5–7·0)
St	6·5 (5·0–8·5)	<0·005	10·3 (7·9–11·9)
Perineal descent (cm)			
R	7·9 (6·6–11·0)	<0·05	10·2 (8·0–12·1)
Sq	7·4 (6·3–9·2)	<0·05	10·0 (7·5–11·0)
St	8·2 (6·4–11·8)	<0·05	10·2 (8·0–12·8)
Anal canal length (cm)			
R	4·3 (2·1–7·4)	<0·05	2·9 (2·0–3·2)
Sq	3·9 (2·0–8·4)	n.s	3·1 (3·0–5·5)
St	3·0 (0·3–8·5)	<0·025	0·6 (0·4–1·6)

R, at rest; Sq, during pelvic floor contraction; St, during attempted defaecation, n.s., not significant

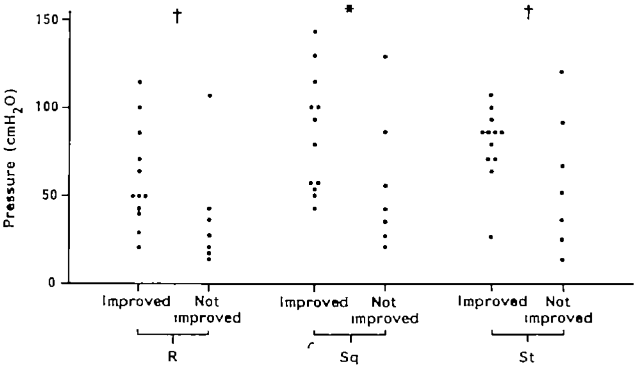

Figure 3 *Pre-operative anal pressure in patients who achieved improved continence and in those who did not R, at rest, Sq, during pelvic floor contraction, St, during attempted defaecation, *P<0·025, † P<0·05 (improved* versus *not improved)*

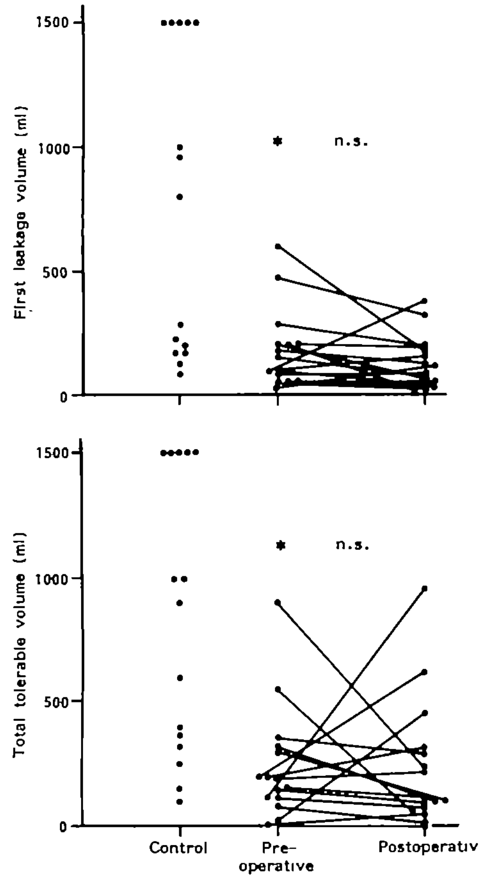

Figure 4 *Saline infusion test before and after operation.* $*P<0.005$ (*pre-operative* versus *control, n.s., not significant* (*pre-operative* versus *postoperative*)

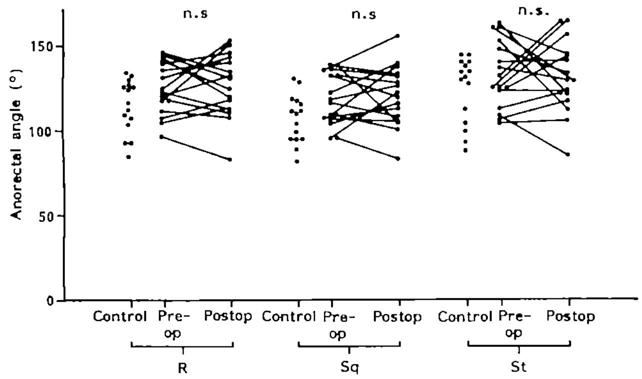

Figure 5 *Anorectal angle before and after operation R, at rest, Sq, during pelvic floor contraction, St, during attempted defaecation, n.s., not significant* (*pre-operative* versus *postoperative*)

potato starch[15]. Balloon proctograms are technically simple and quick[8] but a better outline of the topography of the rectum can be demonstrated using barium mixed with potato starch inserted into the rectum itself[15].

In our study, Baritop mixed with cellulose was used in order to achieve a consistency similar to that of faeces and to obtain a clear outline of the rectum. The anorectal angle was defined as the angle between the luminal axis of the anal canal and the axis of the rectum which was obtained by drawing a line through the anorectal junction and the centroid of the rectum. This method was developed in order to improve reproducibility, as a large interobserver variation has been recorded by us when the posterior margin of the rectum is used for measurement of angles. We found that the pre-operative anorectal angle did not differ significantly from that of the control group and did not change significantly after operation. These findings seem to suggest that the anorectal angle does not play an important role in achieving faecal continence and does not change even after successful postanal repair.

The separation of incontinent patients from controls may be more clearly seen by measurement of the distance of the anorectal junction from the pubococcygeal line[13]. Indeed, pre-operative pelvic floor descent, perineal descent and anal canal length were all significantly different from those in the control group. Furthermore, increased perineal length, pelvic floor descent and a short anal canal length predicted those patients who were not improved by postanal repair. We accept that the number of patients who remained incontinent in this study is small. Nevertheless, videoproctographic parameters appear to be capable of identifying those patients who are unlikely to be improved by postanal repair, where either a permanent stoma or a muscle transposition may be justified[16,17].

Not surprisingly, pre-operative anal canal pressures in patients with faecal incontinence were significantly lower than those of our control group. As has recently been reported elsewhere[18], these pressures did not change significantly after operation. However, low values did predict a poor outcome after postanal repair. Some reports indicate that postanal repair results in a significant rise in resting anal canal pressure or in

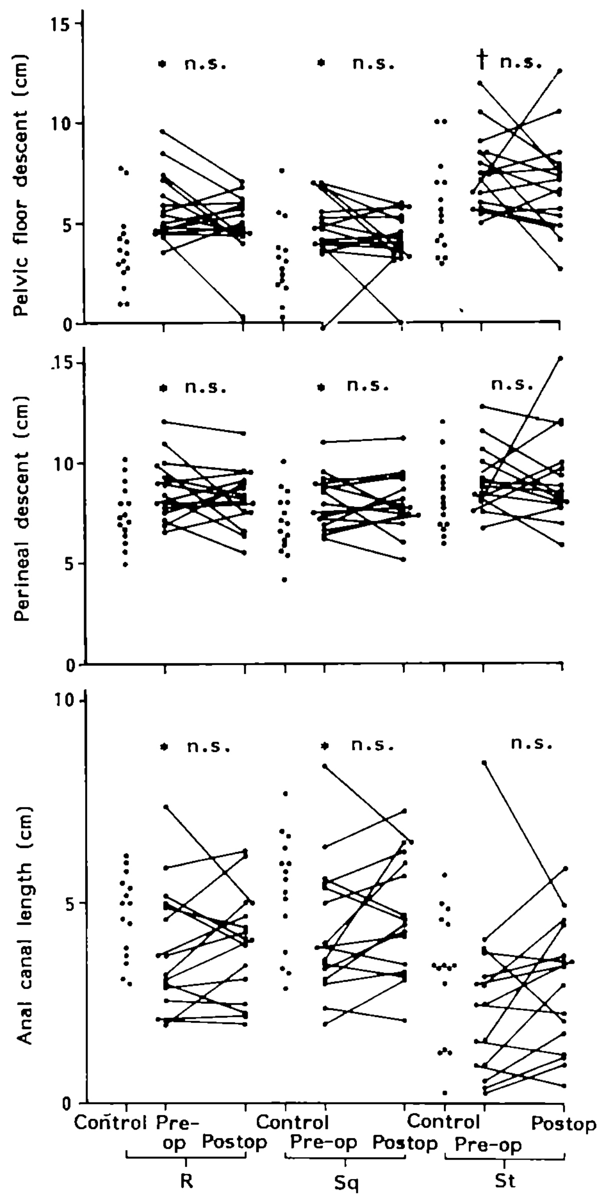

Figure 6 *Pelvic floor descent, perineal descent and anal canal length before and after operation R, at rest, Sq, during pelvic floor contraction, St, during attempted defaecation,* $*P < 0.005$, $\dagger P < 0.05$ (*pre-operative* versus *control*); *n.s., not significant* (*pre-operative* versus *postoperative*)

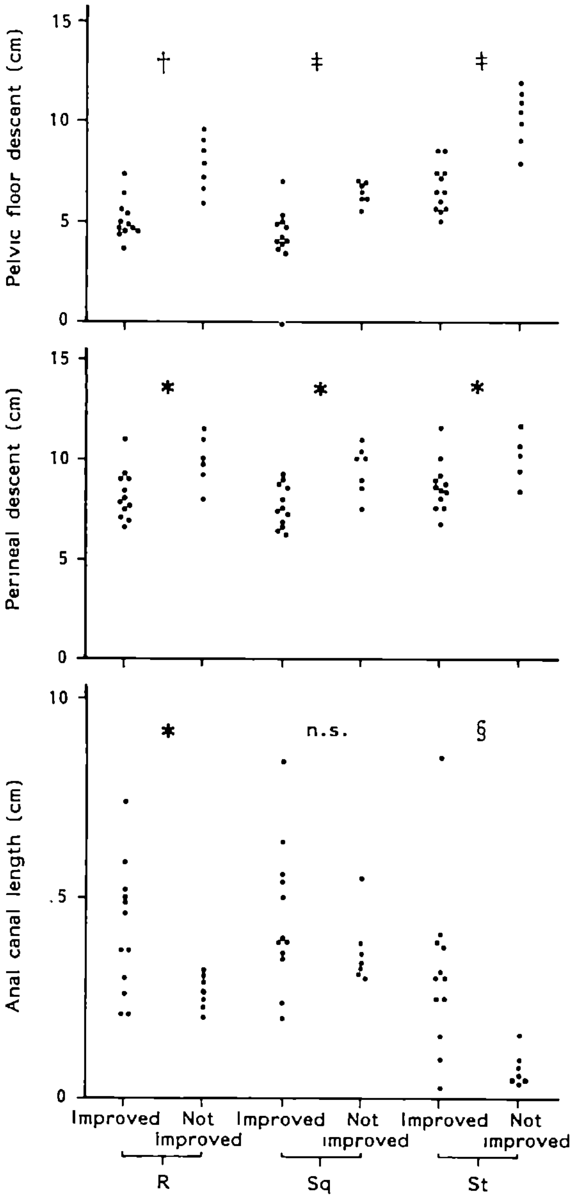

Figure 7 *Pre-operative pelvic floor descent, perineal descent and anal canal length in patients who achieved an improved continence and in those who did not. R, at rest, Sq, during pelvic floor contraction, St, during attempted defaecation,* *P<0·05, †P<0·01, ‡P<0·005, §P<0·025, *n.s., not significant (improved* versus *not improved)*

both basal and squeeze pressures[6–8]. One explanation for this phenomenon may be that the repair protects the internal sphincter from further stretching and increases the efficiency of the pubococcygeus and puborectalis muscles by shortening their effective arc of action[7]. However, the more recent data[18] and the findings of this study imply that sphincter pressures are not improved by the operation, although there may be an increase in the length of the high-pressure zone.

The saline infusion test is used to assess liquid continence[19,20]. In our study, volume at first leakage of saline and total tolerable volume were significantly lower before operation than in controls Surprisingly, results were not improved after successful postanal repair and these parameters failed to predict outcome. Despite these findings a successful outcome was usually accompanied by reduced soiling and continence of liquids. Persistent soiling, however, when it occurred was usually minor and did not necessitate the wearing of pads in patients who obtained clinical benefit.

The incidence of improvement in this small series does not reflect the long-term clinical results of postanal repair which we have reported elsewhere[7] The purpose of this study was to evaluate physiological changes before and after operation compared with normal subjects. Fortunately the clinical results comprise two distinct groups. Those who had a good clinical outcome had no further urgency, did not need to wear pads and were completely continent of solids. Despite this, failure of discrimination and soiling still persisted in a few. The remaining patients all had persistent incontinence to liquids and solids and all continued to wear pads. For this reason we were able to identify physiological parameters which would predict the outcome of operation. These results fail to explain why some patients improve after the operation, apart from the observation that the length of the functioning anal canal is increased following postanal repair.

Pre-operative physiological assessment was found to be helpful in selecting patients who might benefit clinically from the operation. Patients who were not improved were identified by low resting and squeeze anal pressures, abnormal pelvic floor and perineal descent as well as a short anal canal There is now a need to test these parameters prospectively to determine whether results can be improved by an alternative surgical strategy.

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Sex, Enterobius vermicularis and the appendix

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Examination of 182 appendices containing Enterobius vermicularis *demonstrated that male pinworms are seen more commonly than female. There was no association between the sex of pinworms and inflammation in the appendix but inflammation was frequently seen in association with luminal ova. Ova release from female pinworms may be a feature of appendiceal obstruction.*

Keywords: *Enterobius vermicularis*, sex, appendix

The role of *Enterobius vermicularis* (pinworm) in relation to appendicitis has been disputed for over 80 years. At the start of the 20th century, Metchnikoff decided that nematodes were the cause of a large number of cases of appendicitis[1]. Subsequently, Aschoff suggested that pinworms may cause symptoms resembling those of appendicitis but do not cause true appendicitis[2]. This opinion was reinforced by the evidence provided by Hueck[3] and by Gordon[4], but refuted by Duran-Jorda[5] who employed a number of sophisticated pathological techniques to examine appendices containing *Enterobius*. Two reports published in the past year[6,7] have consolidated the idea that *E. vermicularis* appears to have no relationship with acute appendicitis.

In contrast, it is recognized that *E. vermicularis* is one of the least rare nematode causes of inflammatory lesions in the fallopian tubes[8,9]. Histological examination of *Enterobuis* salpingitis shows ova lying in a purulent exudate in which eosinophils often predominate. Occasionally, *Enterobius* granulomas are found within the tube, but in such cases there has probably been a pre-existing partial obstruction of the lumen which has hampered the worm in its passage through the tube, so that it died there, the ova shed during the process causing widespread granulomatous changes[10].

Figure 1 shows the intensity of the purulent exudate seen in a case of *Enterobius* salpingitis. If the female pinworm can cause this degree of inflammation in a fallopian tube then what effect can it have on that other organ which can be obstructed—the appendix? The objective of the present study, therefore, was to establish if inflammatory lesions of the appendix were linked to the presence of female pinworms within the appendiceal lumen. Despite the numerous studies performed on the appendix, the sex incidence of *E. vermicularis* and its relation to inflammation does not appear to have been investigated.

Materials and methods

This study included all appendices containing *E. vermicularis* diagnosed between 1967 and 1987 at two UK teaching hospitals, Leeds General Infirmary, Leeds and St James's University Hospital, Leeds. The methods for examining appendices are similar within the pathology departments of each hospital and junior pathologists rotate between the two departments. Examples of *Enterobius* were sexed by reference to standard textbooks of zoology[11,12]. The numbers of tissue and of pinworm sections were recorded. Acute appendicitis was diagnosed according to standard pathological criteria[13]. Luminal purulent exudate and any other pathology, including the presence or absence of ova, were noted.

Ova seen as a result of artefactual disruption of female worms during sectioning were ignored. Such disruption was easily recognized histologically.

Results

A total of 182 appendices containing *E. vermicularis* were examined. The 182 appendices represent 1·5 per cent of the cumulative total of 12 132 appendices submitted to the two Leeds hospitals between 1967 and 1987. There appeared to be no relationship between appendiceal inflammation and numbers of *Enterobius*. *Figure 2* shows an appendix which contained a total of 161 sections of *Enterobius* but had no evidence of inflammation.

Table 1 lists the sex distribution of *Enterobius* between the three categories of appendix created. It should be noted that there was overlap between two categories: appendices with luminal exudate and those with acute appendicitis; cases of acute appendicitis frequently showed luminal exudate.

The results for each hospital showed a similar trend and have been combined in *Table 1*. In all, 41 cases showed acute inflammation and of these 14 contained ova, whereas only 6 of the 141 uninflamed appendices contained ova ($\chi^2 = 26{\cdot}04$,

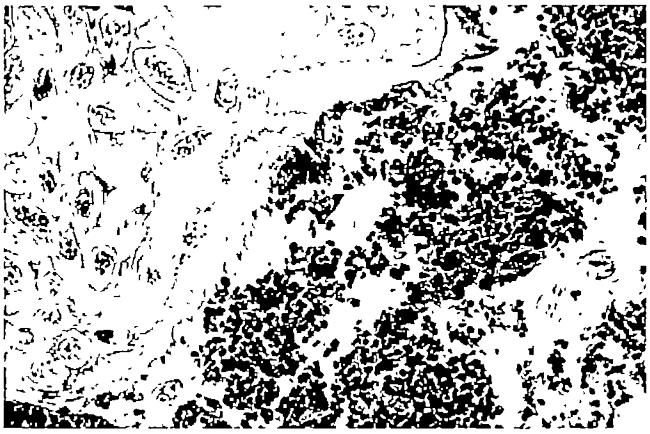

Figure 1 *A gravid female pinworm within the lumen of the fallopian tube. Note the adjacent purulent exudate and ova* (*Stain. haematoxylin–eosin, original magnification* ×*400*)

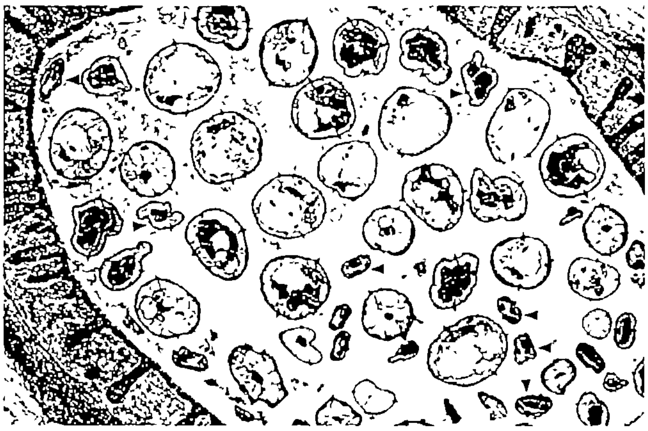

Figure 2 *Male* (*arrows*) *and female pinworms within the lumen of the appendix, inflammation is absent* (*Stain haematoxylin and eosin, original magnification* ×*90*)

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Table 1 *Sex distribution of* Enterobius vermicularis *in 182 appendices*

Category	*n*	Mixed sexes	Male only	Female only	Ova present
Appendices without inflammation	141	39	88	14	6
Appendices with luminal exudate	38	15	18	5	13
Appendices with acute appendicitis	20	9	10	1	6

$P < 0{\cdot}001$). However, there was no apparent relationship between the sex of the *Enterobius* and the presence of inflammation. If appendices containing mixed sexes were excluded, 5 of 26 inflamed, and 14 of 102 uninflamed appendices contained female *Enterobius* (χ^2 *versus* males $= 0{\cdot}16$, P:n.s.).

Only one appendix showed a granuloma The majority of cases of acute appendicitis were seen to occur at the tip of the appendix. Ova distribution was random and was not confined to the tip.

Discussion

The results showed a similar trend in pinworm sex distribution for each of the three categories of appendiceal pathology. These results indicated that there was no relationship between sex of appendiceal *Enterobius* and inflammation It was surprising to note that male pinworms were more commonly seen than females in view of the greater size of the latter. The male size range is 2–5 mm × 0·1–0·2 mm compared with 8–13 mm × 0·5 mm for females[11]. Ova were occasionally seen in appendices containing only male pinworms; presumably female pinworms are present in the appendiceal lumen but are absent from the planes of histological section.

Ova were a statistically significant feature of appendices showing inflammation. Ova were strikingly infrequent in the appendices without inflammation. Ova are not usually deposited in the host's intestine[11] and the presence of ova within the appendiceal lumen is perhaps an indication of partial obstruction of the lumen, as described in *Enterobius* salpingitis. It may be argued that ova have caused the inflammation but there was no supporting evidence for this hypothesis in this study.

The aetiology of acute appendicitis is unknown but many authorities believe obstruction to be the major aetiological factor[14]. This study suggests that in an appendix containing *E. vermicularis* ova are a histological feature of early obstruction. That such obstruction is early may perhaps be deduced from the absence of granulomas.

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Ileal salvage from failed pouches

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Fear that functional failure after proctocolectomy with pouch ormation inevitably means sacrifice of the consequently excised pouch's constituent ileal loops and loss thereby of possibly mportant absorbtive capacity may deter the procedure's performance. We have carried out 25 restorative proctocolectomies, each with quadruple loop (W) pouches and have had o reverse two. In both, the ileum was successfully salvaged.

Results

Table 1 summarizes the patients' details and case histories before pouch excision. Both had required reoperation and pelvic dissection for complications after pouch construction before being driven eventually to request pouch excision for functional failure. Division of the pouch from the anus left a ragged hole (*Figure 1a*) reflected in damage along the cut edge after opening the pouch along its 'seams' (*Figure 1b*), but ileal re-formation was none the less possible (*Figure 2*). A faecal leak occurred in one patient but ceased spontaneously.

Discussion

Pouch failure requiring excision has been reported in 5–10 per cent of large series[1–3]. In our two cases, the ileum has been retrieved and returned to normal function despite extensive pelvic dissection in both, and peripouch sepsis in one.

We use a single layer appositional absorbable suture for making the pouch and used continuous single layer stitching for the ileal reconstruction. Stapling or two layer techniques may render such salvage procedures harder to achieve.

At first glance direct conversion of the excised pouch to a continent ileostomy seems an attractive alternative. Creating the nipple valve however would certainly be difficult and might well be hazardous since we found that tissue stiffness, produced particularly by the antimesenteric suture line, considerably impeded eversion to form the Brooke ileostomy.

Pouches removed for continuing sepsis (in our patient it had been overcome) may well be too damaged for complete success. A considerable part may be recoverable (although perfectly good ileostomy function may follow loss of all 40 cm of terminal ileum) and, with the small, ever present risk in the colectomized patient of bowel strangulation from adhesive volvulus and the possible future desire for conversion to a continent ileostomy, it is arguably beneficial to preserve whatever one can.

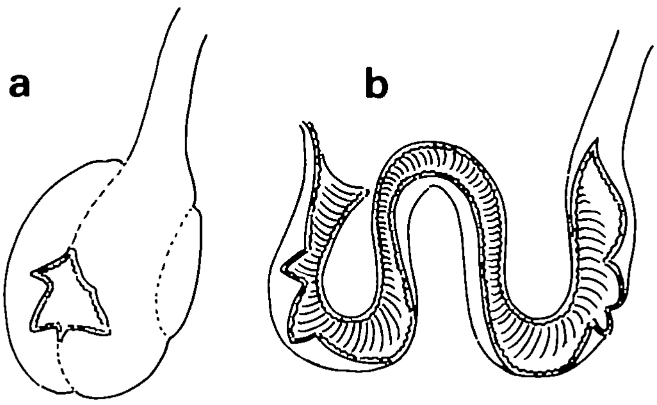

Figure 1 *Appearance of the W pouch **a** after its excision from the pelvis; **b** after division of its 'seams'. Transverse slits and segmental loss from damage during excision can be repaired*

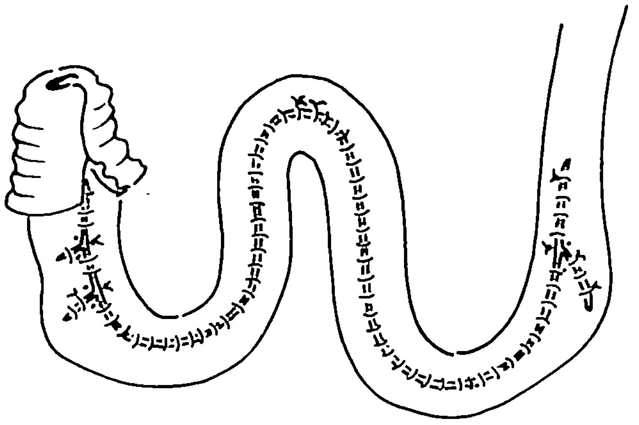

Figure 2 *The terminal ileum restored by a long antemesenteric closure with damaged parts repaired and the spout formed by eversion of the distal end*

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Table 1 *Case histories of two women who required excision of their pouch*

Age (years)	Disease	Associated condition	Procedure	Complications
39	Familial polyposis coli	Chronic drug-treated depression	Proctocolectomy and W pouch	1year postoperatively bilateral oophorectomy for chocolate cysts compressing the pouch
49	Ulcerative colitis	Large fibroid uterus, irritable bowel syndrome	Proctocolectomy and W pouch and hysterectomy	Excessive operative bleeding. Pelvic haematoma evacuated 8 days postoperatively. Pelvic abscess drained 2 months later

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Rectus abdominis muscle flap for persistent perineal sinus

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Persistent perineal sinus is a relatively common complication of rectal excision. There is associated significant morbidity and the surgical treatment is challenging. Conservative measures often fail and radical treatment by wide excision with coccygectomy, distal sacrectomy and skin grafting have been advocated[1,2]. Superior results are reported with insertion of a thigh muscle flap[3-5] following sinus excision, but failure may result from the unreliable vascularity and limited arc of rotation which prevents the flap from reaching the apex of the sinus. This paper describes a rectus abdominis muscle flap which avoids these problems.

Case report

A 64-year-old man with conservatively managed ulcerative colitis for 12 years underwent a proctocolectomy and ileostomy. The perineal wound required re-exploration for abscess formation. Repeated curettage and irrigation failed to cure the sinus A sinogram showed a sinus tract 11 cm in length and no enterocutaneous fistula. He agreed to radical surgical treatment The sinus, extending to the sacral promontory, was excised by combined abdominal and perineal dissection. The left rectus abdominis muscle, isolated on the inferior epigastric vessels, was detached from the costal margin. The upper end was delivered through the dissected tract into the perineum and sutured distally (*Figure 1*) Perineal skin was closed directly over the muscle flap. The peritoneum was closed snugly around the muscle flap and the rectus sheath repaired using a Prolene® suture Prophylactic antibiotics and suction drainage of the pelvis were continued for 5 days Primary healing of the abdominal and perineal wounds was achieved and the patient was discharged 9 days postoperatively Six months after surgery, there has been no recurrence of the sinus.

Discussion

In the management of unhealed perineal sinuses, superior results and lower morbidity are attained by filling the cavity with well-vascularized phagocytically active tissue. Muscle fulfils this principle well[6]. Gracilis[3] and individual hamstring[4] muscle flap transpositions into the perineal defect have been described. They are handicapped by small bulk and precarious blood supply beyond their midpoint as mobilization necessitates segmental vessel division which may render the tip, the most critical segment of the flap, ischaemic. The inferior half of the gluteus maximus, based on the inferior gluteal artery[5], has good bulk and no resultant functional deficit but its length may be inadequate. The rectus abdominis flap[7] avoids these problems and justifies the more extensive abdominoperineal approach.

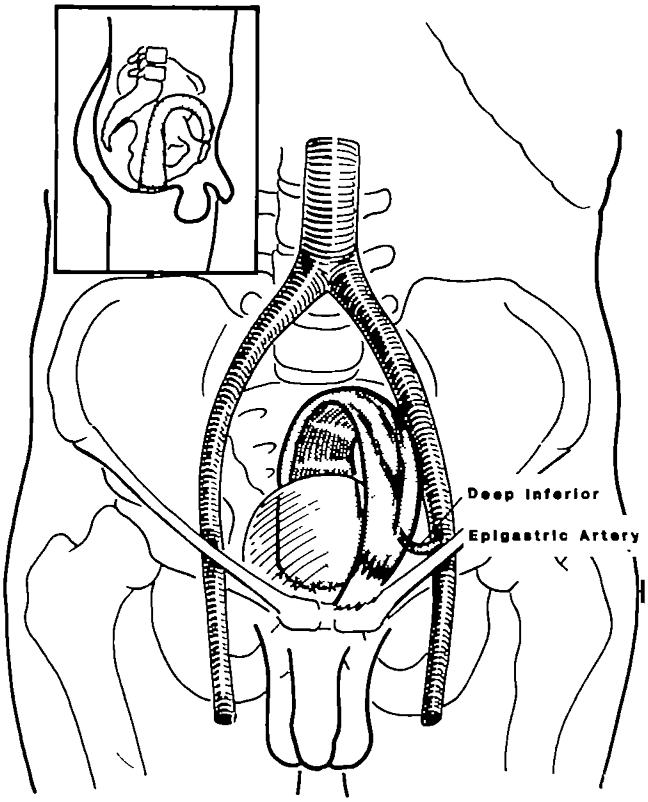

Figure 1 *Anteroposterior and lateral (inset) views showing the dissected left rectus muscle delivered into the pelvis and sutured to perineal skin*

Our preliminary experience with this technique suggests that it may have an important role in the management of this intractable problem.

Acknowledgements

The authors wish to express their thanks to Mr B. Ellis, Department of Medical Illustration, Royal Victoria Hospital, Belfast

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Surgical Research Society Abstracts

The Seventh Tripartite Meeting of the Surgical Research Society held in conjunction with the Society of University Surgeons and the European Surgical Research Society took place on 6, 7 and 8 July 1988 at the University of Bristol. The meeting incorporated the 68th Meeting of the Surgical Research Society. A symposium entitled 'Screening for aortic aneurysm' preceded the free paper sessions. One hundred and ninety papers were ead and the Patey Prize was awarded to Mr D. J. A. Scott for his presentation, entitled 'Application of multiple inear regression in the estimation of peripheral resistance'.

Large scale purification of human islets utilizing a iscontinuous albumin gradient on an IBM 2991 cell separator

S.P. Lake, P.D. Bassett, A. Larkins, K. Walczak, J. Chamberlain, G.M. Rumford, N.J.M. London, P S Veitch, P.R.F. Bell and R.F.L. James, *University of Leicester, UK*

One of the major problems of human islet transplantation as a potential reatment of diabetes is the methodology required for rapid and effective arge scale isolation of viable human islets We have adapted our previously described[1] bovine serum albumin (BSA) gradient isolation method for rat islets to the large scale isolation of human islets by utilizing an IBM 2991 centrifuge, which is in general use for bone marrow transplantation.

Fifteen human pancreata were digested with collagenase and produced a mean (±s.e.m) tissue volume of 11 9±1·1 ml The number of islets obtained after purification was 2645±486 per ml of digest with a purity of 63 6 per cent. The insulin content of the islet preparation was 6·2 per cent of the total digest and was contained in a tissue volume of 30 µl, 3·6 per cent of the original digest Dynamic insulin release of the radient isolated islets was similar to that of non-density gradient isolated islets *In vivo* viability was confirmed by transplantation of diabetic nude rats with prompt reversal of diabetes Mean glucose learance of the transplanted rats was similar to normal (1·6±0 1 *versus* 7±0 2) Purification time was 35±5 min.

This method allows isolation of large numbers of viable islets from he human pancreas.

. Lake SP, Anderson J, Chamberlain J, Gardner S, Bell PRF, James RFL Bovine serum albumin density gradient isolation of rat pancreatic islets *Transplantation* 1987, **43**. 805–8.

The influence of exercise on oesophageal pH and motility in patients with angina-like non-cardiac chest pain

R.C. Stuart, J. Stinson, P.J. Byrne, R.M. Keane, G. Keye, B. Foley and T P J. Hennessy, *St. James's Hospital, Dublin, Ireland*

Coronary angiography is normal in 20 per cent of patients with angina-like symptoms. Oesophageal pathology is present in up to 60 per cent of hese patients. Symptoms are frequently related to exercise We have nvestigated the relationship between exercise and oesophageal pH and motility in 30 patients with angina-like chest pain and normal coronary angiography. After preliminary endoscopy, biopsy, pH monitoring and manometry patients underwent two standardized exercise tests with (a) oesophageal pH monitoring and (b) continuous manometry using a ransducer tipped system

	Reflux oesophagitis ($n=11$)	Nutcracker oesophagus ($n=4$)	Normal oesophagus ($n=15$)
pH Monitoring			
Exercise reflux (n)	5	0	0
Manometry			
wave amplitude mmHg)			
Resting swallows	54 78±3·37	127·75±5·79	63 5±3 6
Exercise swallows	39 8±2·67	†60 4±3·98	52·8±2 73
Resting swallows	*36 6±2 26	130±7 67	70·9±5·65

All values: mean±s.e.m , $^*P<0{\cdot}05$, $^\dagger P<0\ 02$ unpaired students t test

Reflux episodes occurred during exercise in 5 of 11 patients with reflux oesophagitis.

No exercise reflux occurred in the other groups. Oesophageal contraction amplitude decreased significantly during exercise in patients with nutcracker oesophagus and following exercise in patients with reflux oesophagitis No significant fall in contraction amplitude occurred n patients with a normal oesophagus. Reflux and low amplitude contractions indicating poor clearance may explain angina-like symptoms in the reflux group but neither reflux nor alterations in pressure appear to be implicated in nutcracker or normal oesophagus

Distribution of dysplasia in chronic ulcerative colitis (CUC): implications for endoscopic surveillance

B.A Taylor, J.H Pemberton, H. Carpenter, K. Schroeder, D. Wellings, M. Spencer, A.R. Zinsmeister and V.S. Hench, *Mayo Clinic, Rochester, Minnesota, USA*

Mucosal dysplasia may be a marker for the 'at-risk' colon in CUC[1] The aim of this study was to compare the distribution of dysplasia in patients with and without cancer in CUC Fifty patients were identified with cancer in CUC, and matched (for age, sex, disease duration, disease extent and symptomatology) to fifty without cancer All had undergone total abdominal colectomy or proctocolectomy Four biopsies were obtained from eight defined sites within each specimen, using endoscopic biopsy forceps. Biopsies were read 'blind' (H.C.) for the presence and grade of dysplasia Logistic regression was used to assess the association between dysplasia and cancer.

In 26 per cent of cancers, no dysplasia was detected anywhere in the colon. In 60 per cent of cancers > 80 per cent of biopsies were negative for dysplasia Dysplasia was detected in 26 per cent of controls, and was high grade in 2 per cent High grade dysplasia was significantly associated with established cancers (32 per cent; $P<0{\cdot}05$) There was no association between rectal dysplasia and proximal cancer.

There is a difference in the prevalence of dysplasia in the two groups. However, high grade dysplasia seems to be associated with established cancer, while the absence of dysplasia (of any degree) does not exclude it. These findings have implications for surveillance programmes

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Fine-catheter aspiration cytology of peritoneal cavity for the acute abdomen: a randomized sequential clinical trial

R J. Stewart, R.K. Gupta, G.L. Purdie, L.J. Holloway and W.H. Isbister, *Wellington School of Medicine, Wellington, New Zealand*

A randomized sequential clinical trial was undertaken to determine whether fine-catheter aspiration cytology of the peritoneal cavity (FCACP)[1], using the percentage of neutrophils in the sample as the main test marker[2], reduces errors about the need for urgent laparotomy in patients admitted to hospital with acute abdominal pain.

One hundred and forty-four patients with acute abdominal pain were studied Of these, 26 were excluded because the test was unlikely to be useful and 20 did not consent. Conventional clinical assessment was undertaken and then the patients were randomly allocated to have FCACP or not After the test result was made available, the surgeon decided whether to operate or continue conservative treatment The correct decision was later ascertained by a 'blinded' clinical referee

With the entry of the 98th patient the difference between the groups achieved the 5 per cent significance level. The groups were well-matched in regard to demographic and other variables. The decision about urgent laparotomy was incorrect in only 4 of 49 (8 per cent) of the FCACP patients, compared with 14 of 49 (29 per cent) of the others.

It is concluded that FCACP is likely to reduce unnecessary or delayed laparotomies in patients admitted with acute abdominal pain.

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The use of the dorsal genital nerve pudendo-anal reflex for the treatment of neurogenic faecal incontinence

N.R. Binnie, B.M. Kawimbe and A.N. Smith, *Western General Hospital, Edinburgh, UK*

The dorsal genital nerve pudendo-anal reflex is constituted by the afferent dorsal genital nerve (DGN), the conus medullaris and pudendal nerve efferents (S2, S3, S4) to the pelvic floor and external anal sphincter Acute stimulation of the DGN produced a measurable latency response, an integrated EMG external anal sphincter response and a rise in the maximum resting anal canal pressure, establishing the presence of an incomplete denervation, e.g., a neuropathy

This was then followed by chronic stimulation of the DGN in five women with neurogenic faecal incontinence. Stimulation of the DGN was carried out with 1 Hz square wave stimuli 120–150 volts for 5 min 3 times a day for 2 months. This produced an increase in the physiological anal canal length (from 2 4±0 5 cm to 3 2±0 4 cm), the maximum voluntary contraction of the external anal sphincter (from 112±37 cm to 162 cm H_2O) and the maximum resting anal canal pressure (from 57±17 to 94±21 cm H_2O). All subjects regained full continence apart from one with poor control of flatus It is suggested that this technique reinforces the activity of the pelvic floor, is applicable only if the pathways of the reflex are intact, and may correct incontinence of neurogenic causation

Low cystic duct entry predispose to common bile duct stones

P.C. Bornman, R.E. Kottler, J. Terblanche, A.N. Kingsnorth and I.N. Marks, *University of Cape Town Groote Schuur Hospital, South Africa*

In patients undergoing endoscopic papillotomy for bile duct stones, the cystic duct often seems to enter the bile duct low down on the left hand side To substantiate this impression, the site of entry of the cystic duct in patients with bile duct stones was compared with that in patients with stones in the gallbladder, and in a control group.

Endoscopic retrograde cholangiograms (ERCPs) of patients with bile duct stones (BDS) were compared with operative cholangiograms of patients with gallbladder stones (GS) alone, and a control group of patients with abdominal pain and normal ERCPs. Measurements of the bile duct were taken from the ampulla of Vater to the cystic duct entry (CDE), segment 1, the contiguous course of the cystic duct and bile duct (segment 2); and the total length of the bile duct (segment 3). The results are shown in the table

	BDS (*n*=50)	GS (*n*=50)	Controls (*n*=50)	*P* value
Low CDE (3·5 cm) .	28*†	12*	5†	*†<0 005
Low/left CDE	17*†	3*	4†	*†<0·001
Ratio 1:3±s d.	0·28(20)*†	0·54(16)*	0·54(19)†	*†all
Ratio 2·3±s d.	0·43(20)*†	0·21(14)*	0 21(15)†	<0 001

GS *versus* controls = n.s.

The common finding of low and frequently left-sided cystic duct entry in patients with BDS suggests that this may predispose to bile duct stones, possibly by a mechanism of stasis, or by retrograde pressure with gradual dilatation of cystic duct and migration of gallbladder stones[1]

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Influence of high-dose glucocorticoids on histamine release in patients with septic shock

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Glucocorticoids are discussed as inhibitors of histamine release (HR) in different pathological conditions In clinical and experimental septic shock there is a scarcity of data with controversial results. The present study therefore aimed to investigate the influence of high-dose glucocorticoids on HR in patients with septic shock syndromes

From October 1986 to September 1987, 20 patients with septicaemia (entry criteria of the VA Systemic Sepsis Cooperative Study group[1] were examined in a prospective study Of 20 patients 19 were in hyperdynamic status of septic shock when methylprednisolone (MP (2×30 mg/kg body weight, short-term infusion for 20 min, 0 and 4, after entry) was administered. Plasma histamine (fluorometric fluorenzymatic assay) and MP (PHPLC-technique) were determined i parallel continuously over 5 days.

Nine of twenty patients had a significant HR (>1 ng/ml) In 3 of patients the HR was most probably caused directly by MI administration (up to 3 7 ng/ml for about 30 min) The other six patient had HR for other reasons but in five of six patients MP administratio produced further short-term elevation.

High-dose MP given as a short-term infusion can cause HR in th invasion phase. HR could probably be diminished by a slow MI infusion

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Bile acids influence the growth of human breast cancer cells

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Changes in faecal and serum bile acids have been noted in breast cance patients although the relevance of these findings is unknown. Ar investigation into the effects of bile acids on a human breast cancer cell line (MCF-7) has been undertaken and preliminary observations ar reported here.

MCF-7 cells were grown in phenol red free DME/F12 (1.1) cultur medium containing dextran coated charcoal (DCC) treated fetal cal serum (FCS; 5 per cent) for 10 to 12 days before experimentation whic was performed in fresh medium (changed every 48 h) with or withou bile acid addition. DCC treatment (2×1 h at 50°C) of FCS remove endogenous oestrogens and bile acids, and increased exogenous bil acid protein binding capacity (532 µM).

Glycochenodeoxycholic acid (GCDC) stimulated cell growth wit the maximum effect at 100 to 200 µM, while inhibition appeared t occur at concentrations >500 µM and cell death at about 1000 µM (*Table*)

Concentration GCDC (µM)	0	1	10	100	500
Doubling time (days)	2 50	2·11	1·72	1·40	1·84
Thymidine labelling index (%)	20 1	25·6	—	37·7	—
10^4 cells per cm^2 at 8 days	5 2	6 5	10·6	17·1	7 3
10^4 cells per cm^2 at 10 days	6 8	9 3	13·4	19 9	7 9

Bile acid stimulated growth was also seen with glucodeoxycholic acid and glycocholic acid (e.g doubling times = 1·70 and 1 9 at 100 µM) whereas unconjugated bile acids appeared to inhibit growth. Cytosolic oestrogen receptor levels (ERc; Abbott ER-EIA Monoclonal assay) o MCF-7 cells incubated with 100 µM GCDC for 7 days were decrease (−59 per cent±15 (s.e.m) per 10^6 cells).

At a concentration range from normal serum to that found in breas cyst fluid, bile acids appear to stimulate breast cancer cell growth bu reduce the levels of oestrogen receptors

In vivo and in situ tumour aromatase activity in post-menopausal women with breast cancer: effect of 4-hydroxyandrostenedione

M.J. Reed, M.W. Ghilchik, L.C. Lai, A.M Owen, A. Singh, N.G. Coldham, N.A. Shaikh and V.H.T. James, *St. Mary's Hospital Medical School, London, UK*

The contribution that *in situ* tumour aromatase activity, as opposed t uptake from the circulation, makes to tumour oestrogen content is controversial We are therefore carrying out a study using infusion o ^3H-androstenedione (A) with ^{14}C-oestrone (E1) to measure th conversion of ^3HA to $^3HE1$ within tumours. Uptake of oestrogen from the circulation is calculated, and corrected for, using the tissue:plasma ratio for ^{14}CE1 In addition, the overall peripheral conversion of A to E1 and *in vitro* aromatase and DNAα polymerase activities were measured in six postmenopausal women with breast cancer before and after treatment with the aromatase inhibitor, 4-hydroxyandrostenedione (4-OHA). Results from this study show that in most, but not all, tumours a substantial proportion (range 15–89 per cent) of E1 is formed *in situ* Peripheral conversion of A to E1 decreased by more than 90 per cent after treatment with 4-OHA. The level of ^{3}HE1 in tumours decreased by a similar amount while aromatase activity, as measured *in vitro*, decreased by 60 ± 16 per cent in 5 of 6 patients A significant correlation was found between aromatase activity, as measured *in vitro*, and DNAα polymerase activity ($r = 0{\cdot}57$, $P < 0{\cdot}05$) It is concluded that *in situ* tumour aromatase activity can make a significant contribution to the oestrogen content of tumours. Treatment with 4-OHA results in a marked inhibition of both peripheral and tumour aromatase activities.

Relationship between tumour levels of epidermal growth factor and parameters of prognosis in human breast cancer

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Epidermal growth factor (EGF), a potent growth factor, is mitogenic to breast cancer *in vitro*. Although the presence of its membrane receptor in breast tumour has been correlated with poor prognosis, little quantitative information exists on the presence of EGF itself in human breast carcinomas We have therefore developed a radioimmunoassay, to measure tissue levels of EGF and have applied it to a large series of breast tumours.

Eighty-eight breast tumours were analysed for their content of EGF and EGF-R Oestrogen receptor (ER) status, node status and histological grade were also measured.

Of ER positive tumours 59 per cent contained detectable EGF (> 0·1 ng/ml) compared with only 32 per cent of ER negative tumours ($P < 0{\cdot}01$) suggesting a positive correlation. The mean EGF concentration in ER positive tumours was 3·4 ng/ml (s.d. ± 5·8), significantly higher ($P < 0{\cdot}05$) than 1·1 ng/ml (s.d. ± 3·8 ng/ml) found in ER negative tumours. No association was found between EGF and EGF-R status, ER status, node status or histological grade.

The lack of correlation between EGF-R status and ER status found in this study is of interest and contrasts with a previous study[1] The relationship between EGF and ER status has not been previously reported and may be explained by activated ER initiating transcription of the EGF gene.

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Enhancement of cytotoxic effects of Adriamycin® on breast cancer cells: a new action of medroxyprogesterone acetate

N.A. Shaikh, A.M. Owen, K. Patel, M.W. Ghilchik and H. Braunsberg, *St. Mary's Hospital, London, UK*

Pretreatment with oestrogen[1,2] or progestogen[3] may alter responses of breast cancer cells to cytotoxic agents To study possible effects of medroxyprogesterone acetate (MPA) on the action of Adriamycin® (ADR), human breast cancer cells (MCF-7) were exposed to MPA or control medium for 48 h followed by ADR or control medium for 24 h. The washed cells were then allowed to proliferate for 3 days before being harvested and counted. MPA significantly ($P < 0{\cdot}025$ or lower, analysis of variance) enhanced the efficacy of ADR (20 nM) in 4 of 5 experiments. The effect was observed at 10 nM MPA and maximal at 40 nM. Exposure to oestradiol (1 nM) for 24 h before MPA treatment further increased the hormone/drug interaction, while oestradiol followed by control medium (48 h) did not alter the drug effect. A subline of MCF-7 cells resistant to the growth inhibitory effect of MPA[4] responded to the hormone with respect to enhancement of ADR action

MPA increases the cytotoxicity of methotrexate and vincristine[3] as well as ADR. The mechanism of this action is likely to differ from that of oestradiol[1,2] and remains to be investigated. Treatment with MPA immediately before administration of cytotoxic drugs may enhance their effects on breast cancer cells, irrespective of whether the tumour responded to the growth inhibitory actions of the hormone

Adriamycin is manufactured by Farmitalia Carlo Erba Ltd.

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Perioperative cyclophosphamide in the treatment of early breast cancer

J. Houghton, D.L. Riley, R. Nissen-Meyer and M. Baum, *Rayne Institute, London, UK*

Two large randomized clinical trials were designed to evaluate the role of a single course of cyclophosphamide (5 mg kg^{-1} day^{-1} IV) for 6 days immediately following primary surgery for early breast cancer The Scandinavian Adjuvant Chemotherapy Study (SACS-1), initiated in 1965, randomized 1026 patients who have now been followed up for 20 years. Relapse-free survival shows a consistent benefit for patients treated with the perioperative course ($\chi^2 = 11{\cdot}05$, $P = 0{\cdot}0009$) The Cancer Research Campaign Adjuvant Breast Trial (CRC II) exactly repeated the SACS-1 trial but in a 2 × 2 design which also allowed assessment of a 2 year course of tamoxifen. The relapse-free survival at a median follow-up of approximately 4 years shows a trend but no significant benefit for the treated patients ($\chi^2 = 3{\cdot}09$).

Data from the two trials have been analysed together; relapse-free survival according to menstrual status is shown in the table.

	n	O − E	Relative risk	χ^2	P
Premenopausal					
SACS-1	422	−18·26			
CRC II	800	−2·26			
	1222	−20·52	0·83	3·9	0·048
Postmenopausal					
SACS-1	579	−12·50			
CRC II	1195	−17·33			
	1774	−29·83	0·82	5·82	0·016
Overall	2996	−50·35	0·82	9·73	0·002

Similar results were obtained in patients stratified according to nodal status (relative risk, node negative 0·78, node positive 0·86). As the course was well tolerated by most patients, administration of such therapy should be considered in the management of early breast cancer patients.

Ca 15.3: its relationship to clinical stage and progression to metastatic disease in breast cancer

M.J. Kerin, O.J. McAnena, V.P. O'Malley, H. Grimes and H.F. Given, *Region Hospital, Galway, Ireland*

There is increasing interest in the potential role of monoclonal antibodies as tumour markers in the early detection of metastatic disease. Ca15.3 is a circulating antigen which is relatively specific for breast tissue and defined by two monoclonal antibodies. It is elevated in serum of patients with breast cancer, but its relationship to clinical stage and tumour progression has not been defined Ca15.3 levels have been measured in a consecutive series of 97 patients with breast cancer at the time of diagnosis and at 3-monthly intervals thereafter All patients have been evaluated and followed up using routine biochemical and radiological parameters to detect occult metastatic disease

Patients with stage III and IV disease had significantly elevated levels of Ca15·3 (*table*). In all patients with positive bone scans at first presentation serum Ca 15.3 levels were markedly elevated. To date, two

	No of patients	Pre-op serum Ca 15·3 (±s d.)
Benign disease	18	18·0±5·1
Stage I	37	18·4±5·3
Stage II	21	18·0±4·0
Stage III	23	32·0±10·4*
Stage IV	8	155·8±50·2*
Local recurrence	8	23·0±8·0

*$P<0\cdot001$ *versus* stage I, analysis of variance

patients have developed bone metastases on follow-up isotope scans. In one of these patient's serum Ca15.3 was markedly elevated compared with pre-operative levels before detection on bone scan. No patient in this series has demonstrated significantly elevated serum Ca15.3 levels on follow-up in the absence of metastatic disease Ca15 3 is a reliable tumour marker in patients with advanced disease and may be shown to be an alternative to conventional invasive radiological techniques in detecting distant metastases Earlier detection of metastases could facilitate more efficient treatment with adjuvant chemotherapy

Low anterior resection and the intraluminal bypass tube

J.M. Sackier and C.B. Wood, *Hammersmith Hospital, London, UK*

When assessed by clinical, endoscopic and radiographic methods, dehiscence occurs in up to 69 per cent of patients after low colorectal anastomosis[1] A proximal colostomy may fail to prevent this occurring and has associated morbidity and mortality The intraluminal bypass tube is made of surgical grade latex and is sutured to the proximal bowel and traverses the anastomosis. This technique has been used successfully to prevent oesophagogastric dehiscence in experimental animals[2] Fifty-one consecutive patients submitted to low anterior resection of the rectum were randomized prospectively to receive anastomosis with or without the intraluminal bypass tube The anastomosis was assessed radiographically at 7 days

	No.	Clinical leak	Radiographic leak	Colostomy required
Control	26	5	8	3
Intraluminal bypass	25	0*	1†	0

*$P=0\cdot056$; †$P=0\cdot03$, χ^2: Fisher's exact test

The tube was passed on average at 15 days A further 24 patients then underwent the intraluminal bypass operation for anterior rectal resection and there were no leaks in this group. The intraluminal bypass tube reduced the incidence of anastomotic leakage and provided an alternative to defunctioning colostomies

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Use of the end-to-end anastomosis without mucosal stripping diminishes morbidity and time in hospital after restorative proctocolectomy

P.J. Holdsworth and D. Johnston, *The General Infirmary, Leeds, UK*

Major complications are common after restorative proctocolectomy (RP) for ulcerative colitis. Compared with 'mucosal proctectomy' with endo-anal anastomosis (MP+EAA) at the dentate line, end-to-end ileo-anal anastomosis (EEA) is simpler, avoids the need for mucosectomy and creates less tension at the anastomosis Hence, postoperative complications might be fewer and patients' stay in hospital shorter after EEA than after MP+EAA

We report the complications and duration of hospital stay in 50 patients, 25 after EEA and 25 after MP+EAA who underwent RP in the past 4 years The EEA patients were aged a median of 38 years (18–68), and MP+EAA patients, 26 years (16–52). The era of the 'learning curve' was in the preceding 6 years

Sixteen patients (64 per cent) made an uneventful recovery after EEA, but only 9 (36 per cent) did so after MP+EAA ($P<0\cdot05$). After EEA, 21 complications occurred, in 9 patients after MP+EAA, 29 complications occurred in 16 patients. Incidences of anastomotic dehiscence, stricture and small bowel obstruction were all less after EEA than after MP+EAA (n.s.) The lower incidence of complications after EEA resulted in a significantly shorter stay in hospital for the patients median 14 days (11–58), compared with 19 days (12–50) after MP+EAA ($P<0\cdot05$)

Thus, a significantly greater proportion of patients with colitis have an uncomplicated postoperative recovery if mucosal stripping is avoided and end-to-end anastomosis employed. Their stay in hospital is also shorter than that of patients who undergo endo-anal anastomosis

The early detection of recurrent rectal carcinoma by rectal endosonography

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The 5-year survival of patients with recurrent rectal carcinoma is <5 per cent[1] At diagnosis most recurrences are extraluminal and fixed

Rectal endosonography (ES) has been shown to be accurate in the pre-operative staging of rectal cancer[2] We have evaluated ES in the early detection of local recurrence following radical rectal resection.

We performed 143 ES examinations in 92 patients Eighty-seven patients have undergone rectal ES and five female patients who had had abdominoperineal resection of the rectum have undergone vaginal ES, patients' first examinations were performed a median time of 12 months (range 3–115) following surgery

Fifteen of the patients experienced local recurrences all of which were identified by ES In 13 patients recurrence was also demonstrated by digital examination and/or sigmoidoscopy but in 2 patients extraluminal recurrence was identified purely by ES. In each case recurrence was confirmed by histology, or by disease progression.

Earlier detection of locally recurrent rectal carcinoma is possible by the use of endosonography

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Improving surgical excision of colorectal carcinoma using peroperative scanning with ^{125}I-labelled anti-CEA monoclonal antibody

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Previous studies using radiolabelled antibodies to detect the extent of tumour peroperatively have been hampered by only up to a 76 per cent uptake of antibody[1] The use of I^{125} anti-CEA monoclonal antibody (A5B7) injected 4–8 days pre-operatively and scanned peroperatively with a 1 cm cadmium telluride gamma detecting probe has been investigated Histology was correlated with gamma counts detected peroperatively and on the resected specimen of 25 colorectal carcinomas in 23 patients

Of 25 carcinomas, 24 (96 per cent) had an increased tumour· background colon ratio >2·1 with a mean±s e m ratio of 4·0±0·7 *in situ* rising to 5·5±0·8 on the resected specimen owing to the closer proximity of the probe to low rectal tumours after resection. Uptake was independent of serum CEA and was not affected by time from injection The probe correctly predicted whether resection margins were clear in all cases In eight out of ten Dukes' C carcinomas there was a high count over the mesentery In five out of twenty-three patients the results of the probe added information to the operative findings which could influence the surgery performed

Using this antibody 96 per cent of tumours were localized and nvolvement of all resection margins accurately predicted increasing the robability of complete primary resection

O'Dwyer PJ, Sickl-Santarello B, Mojzisik CM, Thurston MO, Martin Jr EW. Intra-operative radioimmunodetection of gastrointestinal neoplasms *Br J Surg* 1987, **74**. 1147.

Differentiation between ulcerative colitis and Crohn's disease sing measurements of proteolytic enzyme activity

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Crohn's disease (CD) differs from ulcerative colitis (UC) in that it causes ransmural inflammation which leads to fistula and stricture formation Abnormal protease activities may be responsible for the lesions in CD and so may be useful as a marker to differentiate the two conditions, a inding which would have a profound influence on surgical treatment, as 20 per cent of patients with rectal and colonic disease are initially misdiagnosed[1].

Full-thickness samples from ileocolic resections were taken and subsamples were assayed for collagenase and cathepsin B activity using a highly sensitive micro-assay developed from standard methods[2,3] CD and UC samples were taken from macroscopically involved tissue while control samples were obtained from macroscopically normal tissue from resections for tumour.

	Median	UQ	LQ	n	Mann–Whitney U	
Collagenase (c.p.m g^{-1} protein)						
Control	64	137	7	16	$P<0.05$	$P<0.05$
UC	142	197	82	11	n s	
CD	177	274	113	7		
Cathepsin B (mol min^{-1} g^{-1} protein)						
Control	0·14	0·18	0·09	22	n.s.	$P<0.05$
UC	0·18	0·27	0·10	8	$P=0.05$	
CD	0·39	0·47	0·28	8		

The increased collagenase activity seen in both CD and UC (*Table*) suggests that it participates in both disease processes, but that it is not esponsible for the clinical and histological differences. The increased median cathepsin B activity seen in CD but not in UC may imply a role or this enzyme in the aetiology of this disease However, the results how a great range of activity within each resection specimen, which precludes any differentiation between CD and UC on the basis of a limited number of samples

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Evidence implicating scavenging of hypochlorite ions by 5 amino salicylic acid as its mode of action in inflammatory bowel disease

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The mode of action of 5 amino salicylic acid (5ASA) in inflammatory bowel disease (IBD) is unknown. We have previously demonstrated marked inhibition of oxygen radical production by neutrophils by 5ASA, when measured by chemiluminescence. Hypochlorite, detectable by luminol-dependent chemiluminescence, is important in the pathogenesis of inflammation In this study, we investigated the possibility that 5ASA acts as a scavenger of hypochlorite

Hypochlorite ions, generated by hydrogen peroxide, peroxidase and chloride, were detected by luminol-dependent chemiluminescence We found 50 μM 5ASA produced total inhibition of control responses The concentration producing 50 per cent inhibition (Ki50) was 0.45 μM Luminol-dependent chemiluminescence produced by 67 μM sodium hypochlorite was totally inhibited by 50 μM 5ASA (Ki50, 0.7 μM).

The fluorescence of 5ASA, excited at 340 nm and emitting at 500 nm, was markedly reduced by either the addition of sodium hypochlorite or by enzymatic generation of hypochlorite by the reaction of hypoxanthine, xanthine oxidase and peroxidase. This suggested that a non-fluorescent product was formed as a result of a reaction between 5ASA and hypochlorite Superoxide and hydrogen peroxide had no effect on the 5ASA fluorescent spectrum

These results show that 5ASA is a specific scavenger of hypochlorite ions, which may explain its mode of action in IBD

An in vitro study of the cytopathic effects of bile acid and pepsin on oesophageal mucosa

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It has previously been shown that high concentrations of bile acid (BA) and pepsin (P) are cytotoxic to oesophageal mucosa *in vitro* Our studies in patients with gastro-oesophageal reflux however, have shown that small quantities of these agents are refluxed into the oesophagus of most patients at night To determine whether these lower concentrations of BA and P are cytotoxic we incubated oesophageal biopsies obtained during endoscopy in normal saline (NS), BA (50, 100, 200, 500 μmol/l) and P (200, 400 μg/ml) for 5 and 22 min periods at pH 2 All specimens were then immediately fixed in glutaraldehyde and examined by electron microscopy. A single blind pathologist assessed each specimen at four different levels for six different parameters (chromatin clumping, cytoplasmic clumping, cytoplasmic vesiculation, cell separation, necrosis and extracellular deposits) using a 0–4 scoring system Minimal structural damage occurred with NS alone at pH 2, whereas both BA ($P<0.001$) and P ($P<0.001$) produced significant cell disruption, cytotoxicity being maximal at 5 min. BA and P produced similar patterns of destruction which was equivalent for the two compounds Small quantities of BA (50 μmol/l) and P (200 μg/ml) produced significant damage ($P<0.001$ *versus* NS) over a short time (5 min)

Physiological concentrations of both BA and P cause similar, non-specific cytological damage to normal oesophageal epithelium over a time duration characteristic of episodes of gastro-oesophageal reflux

Gastric flora in patients with compromised stomach after long hospitalization

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The criteria for the 'compromised' stomach[1–3] include reduced acidity and reduced motility. In the present study we investigate if long hospitalization in patients with 'compromised' stomach leads to installation of nosocomial micro-organisms into the gastric flora. We studied 26 patients who had a mean duration of hospitalization of 16.4 days and met the criteria of 'compromised' stomach Gastric fluid samples for culture were obtained at operation and at the end of the surgical procedure Antibiotic cover was administered IV only after the sampling times The cultures revealed no growth in 13 cases: *Candida albicans* in 5, Gram negative or positive micro-organisms sensitive to common antibiotics in 7, and *Pseudomonas aeruginosa* resistant to most antibiotics (except imipenem) in only 1 case. It is noteworthy that during the 6 months of the study, the resistant strains in our hospital were *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticum* Based on these results we conclude that the gastric flora of patients with compromised stomach even after a long hospitalization is not usually colonized by multi-resistant strains of nosocomial micro-organisms and most probably a potent pre-operative antibiotic cover is not necessary

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The effects of endoscopic laser therapy on oesophageal function

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Endoscopic laser therapy has been used increasingly in recent years with the untested assumption that it provides the best palliation in oesophageal cancer[1]. We have performed a prospective study of oesophageal function following endoscopic laser therapy. Treatment was given with the Nd Yag laser until the gastroscope would pass through the tumour

Four aspects of swallowing were studied

1. The relief of dysphagia was allocated a clinical grade
2. Liquid swallowing was assessed by ^{99m}Tc transit studies
3. Solid swallowing was measured using cineradiology
4. Gastro-oesophageal reflux was measured using 24 h pH monitoring

After endoscopic laser therapy relief of dysphagia was obtained in 50 out of 54 patients (93 per cent) Co-ordinated swallowing for liquids with normal transit times was seen in 22 out of 25 patients (88 per cent) Cineradiology for solid swallowing showed co-ordinated swallowing of barium soaked bread with no hold-up in 10 out of 12 patients (83 per cent). Only 3 of 15 patients showed marginally increased gastro-oesophageal reflux after laser treatment. Initial results did not show any difference between patients with tumours involving the cardia and those with middle oesophageal tumours.

In this group of frail elderly patients endoscopic laser therapy effectively restores and maintains normal swallowing until death without inducing gastro-oesophageal reflux

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Computerized imaging of gastrointestinal sphincters using eight-channel pressure profiles

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Pressure recording to evaluate the function of sphincters is still a matter of discussion. Currently, one channel manometry is done using the perfused open-tip method. Parameters that can be obtained with this technique are sphincter length and maximal pressure without reference to anatomical structures and with an extended range. Pressure recording in eight directions would give less recording variability and could provide a three-dimensional reconstruction of the sphincter

The recordings are done with an eight-channel proble with circular orientated side holes Each channel is perfused by a low-compliance perfusion pump, connected to a transducer and amplifier. Pressure data are digitized, sampled by a computer and stored on floppy disk. Quantitative and qualitative analysis of the recording can be done immediately after the recording. Quantitative analysis includes peak pressure and sphincter length for each channel. Qualitative analysis done by a computer calculates a cylindrical model of the sphincter High sphincter pressures are represented by larger indentations of the cylinder. The model can be displayed as a wire frame, a cross-sectional or a colour representation model. Rotation of the model facilitated instant interpretation

Computerized analysis of manometry was tested in human males. Lower oesophageal and anal sphincter were recorded Eight-channel manometry was shown to have a large reproducibility while the computerized analysis of the pressure data provided immediate insight into the three-dimensional construction of the sphincter.

Gastric adaptive relaxation and symptoms after vagotomy

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Gastric adaptive relaxation (GAR) may be impaired by vagotomy. This effect has been implicated in the pathogenesis of post-vagotomy symptoms, but hitherto no association between impaired GAR and symptoms has been demonstrated.

We measured GAR in 15 healthy volunteers aged 22–41 years (median 30 years) and in 26 patients aged 35–67 years (median 52 years) 6 months to 24 years after truncal vagotomy and drainage (TV+D). Thirteen patients were asymptomatic. The rest had symptoms attributable to post-vagotomy motility disturbances including seve patients with persistent diarrhoea

Fasted subjects were intubated with a Ryle's tube containing pressure microtransducer within a flaccid (800 ml) plastic bag Gastri corpus-fundus pressure was recorded during distension of the bag wit air (15 ml/s) over 30 s. Pressure indices (PI) were derived from th areas under the pressure curves.

Results	PI (cmH$_2$O) Median		Range
Healthy volunteers	12·7		7·5–17·1
Asymptomatic TV+D	14·0	n s.	8·6–16·8
Symptomatic TV+D	17·6	*	11·0–26·8

*$P<0{\cdot}05$ (Mann–Whitney *U* test)

All patients with diarrhoea had abnormal PIs ($P<0{\cdot}01$). PIs fo patients with dumping or bile vomiting were within the normal range

Patients with post-vagotomy diarrhoea have impaired GAR asymptomatic patients do not.

Repeated sclerotherapy or mesocaval shunt for prevention of rebleeding from oesophageal varices—a randomized study

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Sclerotherapy is usually efficient in controlling acutely bleedin oesophageal varices. For prevention of rebleeding several therapeuti modalities are available and in the present study the efficiency c repeated sclerotherapy and mesocaval shunt was compared.

Patients admitted with bleeding oesophageal varices were initiall treated with sclerotherapy After work-up, randomization to repeate sclerotherapy or mesocaval interposition shunt was carried out Sclerotherapy was performed every fourth month with a flexibl endoscope and injection of 1 per cent Aethoxysclerol paravasally. Th study is still in progress and so far 42 patients have been randomized Alcoholic cirrhosis was present in about 75 per cent. Twenty-thre patients have received a mesocaval shunt and nineteen patients hav been subjected to repeated sclerotherapy. The total hospital cost fo each patient at 1987 prices was calculated.

The two groups studied did not differ in respect of age, aetiology o cirrhosis or Child's classification The mortality was 30 per cent in th shunt group with a median survival time of 28 months as compared wit a 47 per cent mortality in the sclerotherapy group and a median surviva of 27 months All the deaths in patients treated with sclerotherap occurred during the first 2 years while in the shunt group death occurred mainly after 2 years of follow up In the sclerotherapy group 1 patients experienced recurrent haemorrhages causing five deaths a compared with the shunt group in which four patients presente postoperative bleeding without associated mortality. The mesocava shunts were patent in 16 of 18 patients investigated at 4 months up to years postoperatively The total hospital costs were similar between th groups

In this study patients submitted to repeated sclerotherapy o mesocaval shunting exhibit similar mortality. The rate of rebleeding i significantly higher in the sclerotherapy group compared with th shunted group. The results are preliminary but suggest that mesocava shunting still may be an alternative for preventing bleeding fro oesophageal varices.

The influence of prostaglandin E$_1$ with volume loading on postoperative pulmonary function

D.B. Hocken, D.A.J. Galvin, P.A. Pate and C.N. McCollum *Charing Cross and Westminster Medical School, London, UK*

Pulmonary dysfunction frequently follows major surgery. The influenc of a peroperative infusion of prostaglandin E$_1$ (PGE$_1$), a poten inhibitor of platelet and leucocyte activation, on micro-embolizatio and subsequent pulmonary dysfunction was evaluated in a porcine model of major aortic surgery

After insertion of arterial and Swan-Ganz catheters 24 pigs were randomized to PGE_1 (100 ng/kg per min) or normal saline as placebo, and Haemaccel® infused to maintain a pulmonary artery wedge pressure (PAWP) of 4–6 mmHg. Standardized aortic surgery consisted of midline laparotomy, small bowel exteriorization, 1·5 h aortic clamping and 1 h shock before resuscitation. Serial measurements of arterial PO_2 (PaO_2), alveolar-arterial PO_2 difference (A-aDO_2), and pulmonary shunt (A–V shunt) were recorded during and 3 days after surgery. Platelet counts and venous aggregate levels measured by screen filtration pressure (SFP) were also recorded.

The mean (±s.e.m.) SFP in placebo animals increased from 0·32±0·04 to 1·55±0·17 during shock with an associated fall in platelet count from 463±94 to 300±81 × 10^9/l ($P < 0.001$). PGE_1 significantly reduced the rise in SFP (0·2±0·04 to 0·64±0·13) and conserved platelet numbers at 405±95 × 10^9/l. Pulmonary function on the third postoperative day deteriorated in all placebo-treated animals compared with pre-operative values ($P < 0.001$). Pulmonary dysfunction (PaO_2, A-aDO_2) was significantly less severe in PGE_1 animals ($P < 0.02$) though the A–V shunt did not reach significance.

	Postoperative pulmonary function (day 3)		
	PaO_2 mmHg	A-aDO_2 mmHg	A–V shunt %
Placebo	79·06±4·69	27·35±3·63	12·95±2·59
PGE_1	93·30±2·41*	14·86±1·39*	6·49±0·33

All results mean ±s.e.m.; *$P < 0.02$ *versus* placebo (Mann–Whitney *U* test)

Prostaglandin E_1 infusion with optimal volume loading reduced platelet consumption, pulmonary micro-embolization and post-operative pulmonary dysfunction following major surgery.

Pressure-controlled reperfusion improves post-ischaemic recovery of LV-hypertrophied rat hearts

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The influence of a pressure-controlled reperfusion (Rp) on metabolic and functional parameters in normal hearts of sham-operated rats and hypertrophied hearts of rats with aortic constriction were studied, the latter being considered to be more susceptible to ischaemia. The hearts were perfused by the Langendorff technique for 30 min at 35°C with Krebs–Henseleit solution and for 5 min at 15°C with St Thomas' Hospital solution, followed by an ischaemic period of 40 min at 15°C. Rp was started abruptly (ARp: 75 mmHg within 1 min) or gently (GRp: 75 mmHg within 30 min) and lasted 45 min.

The tissue levels of metabolites (μmol/g w.w.) and recovery of functional parameters (percentage recovery of initial values) are summarized in the *Table*

	Normal hearts		Hypertrophied hearts	
	ARp	GRp	ARp	GRp
ATP	3·62	3·69	3·18	3·50
SAN = ATP + ADP + AMP	4·83	4·74	4·54	4·71
ECP = (ATP + 0·5ADP)/SAN	0·843	0·868	0·811	0·847
CrP	6·26	7·41	5·07	†6·62
CrP/Cr total	0·444	*0·535	0·380	†0·491
Psyst	73	88	73	85
+dp/dt	73	86	74	87

* $P < 0.05$; † $P < 0.01$

While the mode of reperfusion had no metabolic effects despite some good functional recovery in normal hearts, GRp improved the metabolic state (CrP, CrP/Cr_{total}) as well as the functional recovery in hypertrophied hearts.

A controlled trial of silicone elastomer versus polyurethane catheters for intravenous feeding

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Because of its low thrombogenicity and resistance to infection[1], silicone elastomer has become the favoured material for intravenous feeding catheters, but it is expensive when compared with other materials and is easily damaged. Polyurethane has greater tensile strength, and is cheaper but is not as soft[2]. We have compared silicone elastomer (SE) catheters (Nutricath, Vygon, France) and polyurethane (PU) catheters (Secalon, Viggo, UK) in a randomized controlled manner in 100 patients receiving intravenous nutrition in hospital. The catheters were placed by stab puncture of the subclavian vein and were used exclusively for intravenous nutrition. Feeding solutions were delivered by an infusion pump from a 3 litre bag. Catheters were cared for according to a standard protocol.

The two groups (SE $n = 51$, PU $n = 49$) were well-matched for age (mean 56 *versus* 56 years), sex (30:21 *versus* 31:18), duration of feeding (mean 21·3 *versus* 16·1 days), diagnosis and mean MRC sepsis score (mean 4·4 *versus* 3·9). Complication rates were similarly low in both groups, pneumothorax (SE 1 *versus* PU 0), malposition (2 *versus* 3), clinical infection (0 *versus* 1) and catheter colonization (3 *versus* 2). All were n.s. (Fisher). No thrombotic complications were observed. One silicone catheter ruptured.

We conclude that central venous catheters manufactured from polyurethane are as effective and safe as silicone elastomer catheters for intravenous feeding in hospital and are about half the price.

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Utilization of cyclocreatine phosphate, a functional creatine phosphate analogue, by skin flaps during ischaemia and its ability to sustain phosphagen reserves

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Creatine phosphate (CP) is the major high energy metabolite of skin. Skin flap survival correlates with CP levels and postoperative CP therapy augments flap survival. Cyclocreatine (cC), a functional analogue of creatine, accumulates in various tissues in its functional phosphagen form, cCP. We hypothesized that dietary cC would accumulate in skin as cCP and, because of its more favourable thermodynamic and kinetic properties, would enhance ischaemic tolerance.

cC was synthesized and fed to male DS rats ($n = 24$) admixed 1·5 per cent with standard powdered chow. Control animals ($n = 12$) were fed powdered chow alone. After 3 weeks, standard dorsal skin flaps were elevated in 10 animals from each group, and surviving areas were calculated by gravimetric planimetry. In remaining animals, flaps were studied by regional *in vitro* ^1H and ^{31}P magnetic resonance spectroscopy (MRS).

Flap survival: cC fed = 73·1 per cent, control = 59·9 per cent ($P < 0.005$). MRS revealed prompt depletion of CP in the middle and distal flaps in controls. CP levels failed to recover in the distal third which consistently necrosed. In cC fed animals, dietary cC accumulated as cCP and cCP:CP in all flap regions. cCP was metabolized over a more protracted time course in the middle and distal thirds with eventual recovery in both segments. It is reasoned that cCP is thermodynamically favourably poised to buffer critical falls in ATP for longer periods than CP, thereby providing the requisite milieu for initiation of intrinsic recovery mechanism.

Testicular descent in the fetus—a study of the androgen sensitivity of the gubernaculum

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A number of clinical and experimental observations have suggested that testicular descent is an androgen-mediated process. However, there has been no reported investigation on the presence of an androgen receptor in the gubernaculum.

In this study, tissues were obtained from a total of 248 pig fetuses ranging from 67 to 95 days of gestation. Samples of human benign prostatic hyperplasia (BPH) were obtained at open surgery. Androgen receptor binding was determined by using tritium-labelled methyltrienolone (R1881) with an excess of triamcinolone acetonide to block progestogen receptor binding. The Kd (dissociation constant) and Bmax (total binding) were calculated using 7-point Scatchard analysis.

Cytosolic androgen receptor binding showed no significant difference in Kd between BPH (1·96±1·0), fetal prostate (2·02±1·42) and gubernaculum (2·72±1·68 nmol). However, the Bmax was significantly lower in the gubernaculum (2·4±0·6) than in BPH (28·3±9·0) and fetal pig prostate (24·9±6·5 fmol/g protein). Furthermore, receptor binding with Kd and Bmax similar to that of the gubernaculum was found in five of twelve samples of striated muscle from both male and female pig fetuses.

These results cast doubt on the assumption that the gubernaculum is an androgen-sensitive target organ.

Surgery for benign thyroid disease: pre- and postoperative voice changes

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Although postoperative voice changes after thyroid surgery are recognized, pre-operative assessment of vocal characteristics have not been recorded, or correlated with any changes subsequent to surgical intervention.

We have studied 21 patients with benign goitres before and 3 months after surgical intervention using comprehensive voice analysis and respiratory function tests. These included speech therapy assessments, Visispeech histograms (computer analysis of pitch and voice quality) airways resistance using whole body plethysmography (to correlate voice change with pressure changes across the vocal cords) and tracheal radiography.

Pre-operative voice abnormality was unexpectedly found in 14 patients (67 per cent) on speech therapy assessment and 4 were unaware of any subjective changes themselves. Eight patients with objective postoperative change felt that their voice had improved following surgery, which correlated with speech therapy assessment, and changes in the Visispeech histogram (Mann-Whitney *U* test, $P<0{\cdot}05$). There was no improvement in airways resistance postoperatively with improved speech.

It is clear from this prospective study that subjective postoperative voice deterioration is less common than previously reported, and may even improve. It emphasizes also that it is important to have pre-operative voice assessment as well as indirect laryngoscopy for accurate evaluation of any postoperative speech problems.

Increased prostacyclin (PGI_2) and thromboxane A_2(TXA_2) formation by segments of varicose vein

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Increased urinary metabolites of the anti-aggregatory vasodilator, PGI_2, and the pro-aggregatory vasoconstrictor, TXA_2, have been reported in patients with deep vein thrombosis; however, the tissue of origin is uncertain. As little is known about the formation of PGI_2 or TXA_2 from their common precursor, PGH_2, by varicose veins (VV) we determined the formation of 6-keto-PGF_1 (metabolite of PGI_2) and TXB_2 (metabolite of TXA_2). Segments of normal saphenous vein (NSV) and VV (nine and four patients, respectively) were incubated with 10 μM ^{14}C-PGH_2 for 2 min at 37°C, products were separated by thin layer chromatography. Surface area and mass of NSV and VV were 19±0·5 *versus* 20±0·7 mm^2 and 9·8±0·7 *versus* 11·8±2 mg, respectively. Formation of 6-keto-$PGF_{1\alpha}$ and TXB_2 by the VV was significantly increased over NSV: 164±15 *versus* 260±12 picomoles of 6-keto-$PGF_{1\alpha}$ ($P<0{\cdot}005$) and 22±2 *versus* 38±7 picomoles of TXB_2 ($P<0{\cdot}01$). Thus, VV segments exhibit marked increases in the formation of the anti-aggregatory substance PGI_2 and pro-aggregatory substance TXB_2 suggesting the thrombogenicity of VV is related to an imbalance of the ratio of TXB_2 to PGI_2 rather than absolute numbers. Increased productivity is consonant with other data from stretching of cultured endothelial cells reflecting an increase in PGI_2 production capacity.

Is there really an oxygen diffusion block in lipodermatosclerosis?

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Previous workers have suggested that an oxygen diffusion block exists in areas of lipodermatosclerosis, but have failed to demonstrate this physiologically with oxygen transport investigations. This study measured transcutaneous oxygen tension (P_{tc,O_2}) in 25 patients with venous leg ulcers in air and with 100 per cent O_2 inhalation. All patients had ankle/arm indices of ≥1·0. All measurements were performed with a Kontron 3300 P_{tc,O_2} monitor with the electrodes placed at standard sites on the thigh, foot and lipodermatosclerotic skin. One hundred per cent O_2 was inhaled for 10 min and the rate of change of P_{tc,O_2} was then measured. Results are shown in the *Table*.

	Thigh	Foot	Skin
Rest values (mmHg)	60·8	46·1	24·8*
Peak values (mmHg)	104·9	87·3	46·8*
Rate of change (mmHg/min)	30·9	28·2	16·1*

* $P<0{\cdot}01$ compared to foot, paired *t* test

The rate of increase in P_{tc,O_2} value was significantly lower in lipodermatosclerotic skin compared with normal skin. This method of measuring O_2 diffusion confirms the presence of an O_2 diffusion block and gives a clear understanding of the dynamics of tissue oxygen diffusion in venous ulceration which effectively appears to render the superficial dermis ischaemic.

White cell and platelet accumulation as a possible cause of venous leg ischaemia—a new hypothesis

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Three groups of fifteen subjects were studied: normal controls, patients with primary varicose veins (VV), and patients with proven deep venous insufficiency (DVI). Serial venous samples were taken from a cannula inserted 5 cm above the malleolus in the supine and sitting positions. Red cell (RBC), white cell (WBC), and platelet (PC) concentrations were measured in each sample.

Controls and patients with VV showed similar results. In patients with DVI there was a significantly greater increase in RBC in the sitting position than in the other two groups ($P<0{\cdot}01$). There was also a significant ($P<0{\cdot}01$) loss of WBC in the dependent leg of DVI patients—28 per cent mean decrease in WBC after 60 min. This was reversed, with a 'washout' of WBC when the patients resumed the supine position. There was a parallel ($r=0{\cdot}82$) decrease in PC draining the dependent leg, but no washout after resuming a supine position.

Venous hypertension is associated with abnormal capillaries surrounded by a 'fibrin-cuff'[1]. Our results support the hypothesis that at low capillary perfusion pressure plugging by WBC, accompanied by platelets which are known to be abnormal in DVI[2], may play an aetiological role in venous ulceration.

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Haemodynamics of carotid patching: an angiodynographic study

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Vein patch angioplasty has been proposed as a technique for reducing the incidence of recurrent carotid stenosis. Late restenosis is due to recurrent atherogenesis, which in turn is promoted by reduced wall shear stress. The impact of vein patching on carotid bifurcation wall shear stress is unknown.

We used colour-coded Doppler flow imaging (angiodynography) to assess the flow characteristics of 46 postoperative carotid bifurcations (27 patched; 19 unpatched) in 39 patients. Vessel dimensions, Doppler shift frequency, peak systolic velocity, volume flow and flow profiles were recorded. Peak systolic carotid bulb flow reversal (blue), which reflects wall shear stress, was expressed quantitatively as a percentage of the vessel diameter.

Four patients developed significant (> 50 per cent) restenosis (2 patched; 2 unpatched). Angiodynography demonstrated significantly ($P < 0·05$) larger carotid bulb diameters in the patched group (patched 11·0 ± 0·4; unpatched 8·6 ± 0·4). Increasing bulb diameter was significantly correlated with increasing flow reversal ($r = 0·46$, $P < 0·001$). Finally, patched vessels demonstrated significantly ($P < 0·05$) more flow reversal than those closed primarily (patched 46·0 ± 3·6; unpatched 31·3 ± 4·8).

These results suggest that vein patching causes reduced wall shear stress. This might in turn be an important factor in the development of late recurrent carotid stenosis.

Simultaneous response to carbon dioxide inhalation of middle cerebral and internal carotid artery blood flow velocity peak frequency

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The degree of response of the cerebral circulation to carbon dioxide inhalation is considered to indicate a measure of reserve capacity[1].

A study has been undertaken to assess the relationship of blood flow in the middle cerebral (MCA) and internal carotid (ICA) arteries in response to inhalation of 5 per cent carbon dioxide. Simultaneous peak frequencies in both arteries were recorded using transcranial pulsed and continuous wave Doppler with continuous monitoring of end expiratory pCO_2. Results were expressed as a reactivity index where

$$R = \frac{\%\ \text{change peak frequency}}{\text{unit change end expiratory } pCO_2}$$

Subjects were divided into normal and those with either unilateral or bilateral carotid disease (*table*).

	No	Mean age (range)	Artery	Mean reactivity (s.d.)	Correlation coefficient	*P* value
Normal	14	37	ICA	16·40 (6·32)	0·508	0·0095
		(21–70)	MCA	20·42 (9·42)		
Unilateral	8	61	ICA	14·17 (7·15)	0·744	0·0022
		(42–80)	MCA	18·10 (7·60)		
Bilateral	9	62	ICA	9·67 (5·04)	0·257	0·5039
		(52–72)	MCA	12·77 (7·36)		

MCA reactivity was consistently greater than ICA reactivity in all groups (*t* test $P = 0·0045$). Results showed a statistically significant correlation between ICAR and MCAR in normals and those with unilateral carotid stenosis but no correlation in those with bilateral disease. MCAR and ICAR were not correlated to the degree of ICA stenosis judged by the peak frequency within the stenosis. These results suggest that MCAR is a better indicator of cerebral blood flow reserve and that response to CO_2 inhalation is often maintained even in the presence of severe carotid disease.

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Eicosanoid metabolism after carotid endarterectomy in a non-human primate model: effects of low- and high-dose aspirin

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Aspirin is currently recommended for patients undergoing carotid endarterectomy. However a benefit has not been established for either high-dose aspirin, or for a low aspirin dose which selectively inhibits platelet cyclo-oxygenase while sparing vascular prostacyclin production. We have defined a selective dose of aspirin in *Macaca fascicularis* monkeys similar to that seen in man. Two weeks before bilateral carotid endarterectomies, 7 monkeys were treated with selective low-dose aspirin (LDA) (1·2 mg/kg per day), 6 monkeys were treated with non-selective high dose aspirin (HDA) (12 mg/kg per day) and 10 monkeys served as controls (C). (Platelet reactivity was monitored by serum thromboxane B_2 levels and bleeding times.) At surgery one carotid artery was excised, endarterectomized, and perfused for luminal production of prostacyclin (6-keto-$PGF_{1\alpha}$). The contralateral carotid artery was endarterectomized, flow re-established, and excised 6 weeks later.

	Bleeding time (min)	Prostacyclin (pg/mm^2 per 15 min)	Patency
C	3·6 ± 0·6	15·9 ± 2·0	50%
LDA	6·0 ± 0·7*	17·2 ± 1·3	100%*
HDA	6·5 ± 0·5*	1·6 ± 0·8*	100%*

mean ± s.e.m., * = $P < 0·05$ *versus* control

This study demonstrates that both selective and non-selective aspirin are good antithrombotic agents and improve early patency after endarterectomy. Low-dose aspirin provides this selective benefit without the inhibition of vascular prostacyclin production seen with higher doses of aspirin. Low-dose aspirin may be associated with better long-term patency due to a more optimal eicosanoid balance.

Do platelets play a role in failure of balloon angioplasty?

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Early thrombosis or late restenosis may occur in up to 45 per cent of femoropopliteal balloon angioplasties. As platelet accumulation at dilatation sites may play a role in failures, we have investigated radiolabelled platelet accumulation following angioplasty.

Twenty patients (44–85 years) with severe lower limb ischaemia and angiographically demonstrated occlusion or stenoses were selected for angioplasty. Autologous ^{111}In-labelled platelets were injected before angioplasty and gamma images performed before 1, 24 and 48 h after angioplasty. Serial ankle Doppler pressure and platelet accumulation determined by radioactivity counts at angioplasty and reference sites and expressed as a radioactivity ratio were made.

Fourteen of the twenty angioplasties involved complete occlusions including four iliac and sixteen femoropopliteal lesions. Platelet radioactivity at angioplasty sites increased from predilatation values of 1·08 ± 0·06 to 2·06 ± 0·27 at 1 h ($P < 0·01$), 1·84 ± 0·26 at 24 h ($P < 0·01$), and 1·69 ± 0·27 at 48 h. Maximum platelet uptake of 3·01 ± 0·55 in subsequent failures compared with 1·89 ± 0·26 in successful dilatations (n.s.). The results are expressed as mean ± s.e.m.: statistical analysis, paired Wilcoxon test.

Balloon angioplasty results in early platelet accumulation, this was greatest at 1 h and may initiate subsequent failure following angioplasty. Platelet manipulation before and after angioplasty may reduce failure rate.

Experimental interventional venous angioscopy—what price for vision?

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This study compares valvulotomy performed by an instrument delivered through the angioscope *versus* the standard technique used in the *in situ* bypass.

Eighteen mongrel dogs (≈ 20 kg) were anaesthetized and both femoral veins were exposed from groin to knee. A 2·8 mm diameter angioscope was passed through the saphenous vein to the common femoral vein valve. An angiographic catheter armed with an experimental hook was used to cut the valve cusps under direct vision. The hooked catheter was passed through one of the angioscope ports. On the opposite side, a Mills valvulotome was inserted through the saphenous vein and blindly cut the valve. Operative time was recorded and difficulties noted. Bilateral venography, sacrifice, and common femoral vein salvage for histology was performed immediately, at 2, 7, 21 and 42 days.

Variable	n	Angioscope	Mills	P<
Operation time (min)	13	8·0±3·7	0·8±0·4	0·001*
Venogram (open)	18	12	14	n.s.†
Histology (disease free)	18	9	15	0·05†

* Student *t* test; †χ^2 test

Both techniques effectively cut the valves shown as hyalized fragments by histology. The angioscopic technique demonstrated more venous damage and required more time (*table*)

The cost of angioscopically directed valvulotomy in small veins may be too great for *in situ* bypass conditions

Blood transfusion immunomodulation and age in the rat

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Blood transfusion (BT) may have a detrimental effect on the survival of colonic cancer patients. The Sprague-Dawley rat carcinogenesis model provides a useful method of investigating colonic cancer. The aim of this research was to assess the influence of BT on peripheral T cell subsets in the Sprague-Dawley rat.

Sprague-Dawley rats were given three weekly transfusions of allogeneic (DA) blood and controls were given NaCl 0·9 per cent Pre- and post-transfusion peripheral T lymphocyte subsets were enumerated using monoclonal antibodies and flow cytometry After BT normal young rats did not show a significant change in T cell subsets (*Table*) Aged rats had an increase in OX8 T cells which suggests suppression of cell-mediated immunity. Transfusion with NaCl was not associated with a similar effect. These results suggest that older subjects may be more susceptible to the immunomodulatory effects of blood transfusion

Effect of BT on T lymphocyte subsets in normal rats—paired data

	mean % cells labelled (s.d.)		
	monoclonal antibody		
	W3/13	W3/25	OX8
A. 16-week old rats			
pre-transfusion, $n=14$	76·7 (8·9)	37·6 (8·4)	36·3 (7·6)
post-transfusion	67·7 (7·1)	32·9 (7·1)	36·5 (11·5)
P value *t* test	0·006	0·13	0·97
B. 36-week-old rats			
pre-transfusion, $n=6$	63·3 (7·8)	23·1 (7·1)	37·5 (7·7)
post-transfusion	69·3 (7·2)	23·8 (5·8)	47·2 (6·4)
P value: *t* test	0·26	0·84	0·039

Is blood transfusion induced augmentation of tumour growth a result of decreased natural killer (NK) cell activity?

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Despite conflicting evidence concerning the importance of immunosurveillance in controlling human cancer, the phenomenon of transfusion induced immunosuppression has resulted in studies to investigate the potential deleterious effect of blood transfusion in cancer patients

In a C3H mouse fibrosarcoma model (UV-2237) we have demonstrated that transfusion with allogeneic blood results in a significant augmentation of both spontaneous and experimental metastases. As UV-2237 is natural killer (NK) sensitive *in vivo* the effect of blood transfusion on NK activity was therefore investigated with a lysis assay using ^{51}Cr-labelled Yak-1 cells as targets. Effector cells were from spleens of C3H mice which had been transfused 14 days previously with 0·25 ml of C57B16 blood. After 4 h target lysis was decreased in the transfused animals compared with non-transfused controls, reflecting a decrease in splenic NK activity Furthermore, following intravenous inoculation of radioactively labelled Yak-1 cells, transfused animals had a statistically significant increase in lung radioactivity after 2 and 4 h compared with non-transfused controls (*table*), implying that destruction of the NK sensitive target cells was impaired in the transfused animals.

Table *Effect of blood transfusion on ^{51}Cr Yak-1 clearance from lungs (c.p.m. ± s.d.)*

Time (h)	No transfusion	Transfusion
2	16 629±4923	25 698±3506*
4	4706± 940	11 959±1033*

* $P<0·05$ Student's *t* test (6 animals in each group)

In conclusion, allogeneic blood transfusion results in decreased NK activity in a mouse model, and this may contribute to augmentation of tumour growth.

The inhibition of lymphokine-activated killer cell generation by tumour cell lines *in vitro*

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Stimulation of peripheral blood mononuclear cells (PBMC) with interleukin 2 (IL-2) results in the generation of lymphokine-activated killer (LAK) cells which are highly cytotoxic towards tumour cells *in vitro* Re-infusion of autologous LAK cells and IL-2 into patients with malignant disease results in tumour regression in some patients However, LAK generation is impaired in patients with advanced disease[1] and infusions of IL-2 alone are ineffective. Since tumour cells may be immunosuppressive we have studied the effects of tumour cells on LAK generation. Tumour cells were obtained from the cell lines G361 (malignant melanoma), COLO 320 and HT-29 (colorectal cancer) and SKBr3 (breast cancer) Control cells included umbilical cord vein endothelium, normal colon and breast epithelium, and allogenic or autologous lymphoblasts. Normal human PBMC were stimulated for 4 days with 1000 units IL-2/ml in the presence and absence of tumour cells or control cells at a PBMC inhibitory cell ratio of 50:1. LAK cytotoxicity (lytic units) was measured on day 4. The results were as follows. (mean ± s.e.m. of *n* experiments)

'Inhibitory' cell	NIL	G361	COLO320	HT29	SkBr3	cells
n	28	21	4	4	9	10
Lytic units	57·5 ±11·7	21·1 ±6·6*	12·5 ±5·5*	15·2 ±2·3*	63·4 ±14·7	55·1 ±8·1

NIL, no added tumour cells

G361, COLO320 and HT-29 inhibited LAK generation (*$P<0·05$) and were even more inhibitory after treatment with interferon-γ suggesting the involvement of an inducible protein. The presence of 20 per cent supernatant from the same cell lines (but not SKBr3 or control cell supernatants) almost completely inhibited LAK generation (mean ± inhibition = 99·8 per cent ± 0·2 per cent) Thus some tumour cells and/or their soluble products inhibit LAK generation This may explain the impaired LAK activity in patients with advanced disease and the therapeutic failure of IL-2 alone.

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Interleukin 2 (IL-2) production and IL-2 receptor expression of lymph node lymphocytes draining large bowel cancer

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Interleukin 2 (IL-2) is required for the maturation of T lymphocytes and development of cytotoxicity to tumour cells.

Lymph nodes draining six colorectal cancers and draining eight enign colons were taken at laparotomy. Lymphocytes were harvested, abelled with monoclonal antibodies for lymphocyte sub-sets and IL-2 receptor status, measured by flow cytometry: for remaining ymphocytes, basal and phytohaemagglutinin (PHA) stimulated IL-2 roduction was measured by bioassay.

	pan T (%)	Helper inducer (%)	Sup-pressor cytotoxic (%)	IL-2 receptor (%)	Basal IL-2 pro-duction (units/ml)	PHA stim IL-2 pro-duction (units/ml)
Benign ($n=8$)	54·4 ±13·8	40·4 ±17·7	16·1 ±8·2	1·33 ±1·5	0·46 ±0·4†	145 ±0·4†
Malignant ($n=6$)	55·8 ±14·9	39·3 ±19·8	18·6 ±9·0	0·89 ±1·0	0·16 ±0·2	118 ±107*
P value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Values are mean ± s.d. pan T, all T lymphocytes.
*$P<0{\cdot}05$; †$P<0{\cdot}01$

There was no significant difference in percentage of total lymphocytes or lymphocyte subsets in lymph nodes draining colorectal cancer or benign colon. IL-2 receptor expression, basal and stimulated IL-2 production were similar in patients with cancer and benign disease.

Lymphocytes from lymph nodes draining benign and malignant large bowel showed considerably enhanced IL-2 production ($P<0{\cdot}01$, $P<0{\cdot}05$ respectively) after stimulation *in vitro* with PHA.

These data suggest that lymphocyte subsets and IL-2 production are preserved in lymph nodes draining colorectal cancer and that these lymphocytes are capable of further stimulation by extrinsic agents which may improve the host response to tumour

Expression and localization of the c-erbB-2 protein product in colonic neoplasia

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Multiple copy numbers of the c-erbB-2 gene have been reported in numerous cases of adenocarcinoma implicating this putative growth factor receptor in neoplastic progression. In a survey of 40 colon carcinomas we have found no evidence of amplification or gross rearrangement of the c-erbB-2 gene in Southern blot analysis, yet immunohystochemical studies using a polyclonal antiserum[1] revealed a wide range of staining for the protein product in sections from these tumours. Staining can be competed out by the original peptide immunogen and correlates with tumours known to over express the 185 000 molecular weight protein product. The elevated levels of the c-erbB-2 protein product are clearly not modulated at the level of DNA copy number but at a later stage in synthesis Immunocytochemical studies on normal colonic mucosa have demonstrated localization of the putative c-erbB-2 receptor at the surface of crypts with no staining observed within crypts. In contrast, 'normal' tissue adjacent to carcinomatous regions displayed a distribution throughout the crypt even when the tumour showed an absence of antibody staining. Pre-neoplastic lesions stain in a similar manner to that of mucosa adjacent to tumour. The contrast in staining between tumours and the adjacent 'normal' tissue suggests an aberrant distribution of the c-erbB-2 protein associated with pre-neoplastic change in colonic mucosa.

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Lymphocyte subsets and natural killer cells in lung cancer tissue: its relationship with blood percentages

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Infiltration of immunocompetent cells in malignant tissues can play an important role in the host-immune response against cancer but few clinical studies have been reported The purpose of the present paper is to investigate the presence of CD4 (T-helper lymphocytes), CD8 (T-cytotoxic/suppressor lymphocytes) and antileu7+(NK cells) in neoplastic tissue (TIL) of patients with lung cancer, and its relationship with the percentage of these cells in peripheral blood (PBL).

Fifteen males with primary lung cancer (3 adenocarcinoma, 9 squamous, 2 large cell and 1 alveolar cell carcinomas stages II and III) were studied Using monoclonal antibodies both PBL and TIL were determined by means of flow cytometry and an immunohistological analysis[1], on the day of surgery χ^2, Spearman's and Student's t tests were used as statistical methods. CD4/CD8 ratio in TIL was correlated with CD4/CD8 ratio in PBL ($P<0{\cdot}02$). A significant increase of CD8 cells and a CD4/CD8 ratio < 1 was associated with poorly differentiated cell tumours ($P<0{\cdot}05$). Antileu7+ cells were observed in all cases, but none of the above mentioned correlations were found. T-cytotoxic/suppressor cells seem to play a predominant role in the host-immune response against lung cancer, while the role of natural killer seems secondary Our results are in agreement with Harabuchi's observations in head and neck cancers[2].

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Changes in crypt cell production rate in adapting colonic epithelium

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The cell birth rate in colonic epithelium may reflect an individual's long-term susceptibility to developing colorectal cancer[1] Extensive small bowel resection in rats increases both colonic crypt cell production rate (CCPR) and experimental tumour yield, whereas colonic defunction reverses these effects[2]. CCPR was measured in organ-cultured mucosal biopsies taken from the upper rectum of patients with jejunoileal bypass (JIB) for morbid obesity ($n=9$) and patients with Hartmann's procedure ($n=7$), and results were compared with control patients with haemorrhoids ($n=16$). Crypt width was determined during microdissection by a modular image analysing system. After JIB CCPR rose by 105 per cent (12·80 ± 2·67 *versus* 6·23 ± 1·49 cells/crypt per h $P<0{\cdot}001$) and there was an 18 per cent increment in crypt width ($P=$n.s.) In patients with rectal defunction CCPR was less than half that of controls (1·96 ± 0·68 *versus* 4·65 ± 0·54) cells/crypt per h: $P<0{\cdot}0001$) and crypt width fell by 38 per cent ($P<0{\cdot}0001$). Both JIB and Hartmann's procedure have profound and persistent effects on mucosal cytokinetics Diarrhoea that follows colostomy closure may be due to adaptive hypoplasia Patients with JIB may be a high-risk group for developing colorectal cancer and should be kept under close surveillance.

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Assessment of colonic cytokinetics by metaphase arrest by organ culture

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In vivo stathmokinetic measurement of intestinal crypt cell production rate (CCPR) is a precise method of assessing mucosal proliferative rates in rats[1], but is unethical in man. Colonic explants can be cultured *in vitro* in order to determine CCPR, but it is not known if values reflect those *in vivo*. CCPR in the descending colon of Sprague-Dawley rats ($n=57$) was determined simultaneously by a standard *in vivo* technique (using IP vincristine ($n=28$)) and an organ culture method ($n=29$) Rats had either 80 per cent jejunoileal bypass (JIB), or had colonic defunction or acted as controls

Group	CCPR *in vivo* (cells/cryps per h)	CCPR after 18 h culture (cells/crypt per h)
Control	4·62±0·39	4/80±0·23
80% JIB	7·81±0·71*	6·75±0·72†
Defunctioned	2·11±0·39*	1·81±0·35†

* $P<0·01$ *versus in vivo* controls
† $P<0·02$ *versus* organ culture controls

After 18 h organ culture explants were well preserved. The 80 per cent JIB caused a 41–65 per cent increment in colonic CCPR whereas after defunction CCPR fell by 56–62 per cent By comparing CCPR between *in vivo* and *in vitro* groups, no significant differences were found in control or adapting colonic mucosa. Organ culture is a satisfactory and valid method of measuring colonic CCPR, and values obtained in man *in vitro* may accurately reflect cytokinetic parameters

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The reproducibility of ambulatory pH monitoring

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Oesophageal pH monitoring is increasingly used in the diagnosis of gastro-oesophageal reflux (GOR) and to monitor the effects of treatment, however the reproducibility of current techniques is unknown The aim of this study was to investigate the reproducibility of ambulatory pH monitoring (pHM) in patients and control subjects.

We studied 35 patients (12 women) with frequent GOR symptoms, mean age 45 years (range 22–69 years) and 5 asymptomatic controls (1 woman), mean age 31 (range 19–56) After initial oesophageal manometry all subjects underwent standardized pHm on day 1 (period 1) and again between 5 and 28 days later (period 2) (Ormed ambulatory system). Restrictions were placed on medication, diet, smoking and alcohol. The recording period was 22 h. All subjects were fully ambulant at home. Analysis of the recording was at pH levels 3·5, 4·0, 4·5 for percentage reflux time and reflux episodes Statistical analysis was by the *t* test and analysis of variance

The results at pH 4 for total percentage reflux time and reflux episodes longer than 5 min (±s.e.m.) are shown in the *table*.

	Period 1		Period 2	
	Total %	RE>5 min	Total %	RE>5 min
Patients	15·3±3·3	7·7±1·5	15·6±2·7	10·1±1·7
Controls	4·1±0·9	3·0±0·8	5·1±1·3	2·8±1·0

RE, reflux episodes

Patients had more acid reflux than controls ($P<0·05$) There was significant correlation ($P<0·01$) between corresponding values in the patient group at all pH levels examined. The coefficient of variation improved with increasing pH level In general pHm is a reproducible investigation.

A new perspective in oesophageal motility: 24-h ambulatory oesophageal manometry

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Oesophageal manometry is limited by sampling motility over a short time period. To overcome this limitation, 24-h ambulatory manometry was performed with two transducers placed 5 cm apart in ten normal subjects and six patients (two with diffuse spasm, four with nutcracker oesophagus) Automatically 2 min samples of motor activity were stored every 34 min while the individual was upright and alert or supine and asleep. Patients and subjects were also instructed to consciously initiate samples; the latter every hour, the former during symptoms. Peristaltic and non-peristaltic (simultaneous and isolated) waves were identified by measuring the time delay between transducers

Normal subjects had a continuous motor activity consisting of 1·3±0·7 peristaltic and 0·6±0·3 non-peristaltic waves per sample The non-peristaltic background activity was not affected by the degree of consciousness, asleep, awake, or during initiated samples The number of peristaltic waves increased significantly with increasing states of consciousness 0·5±0·3 asleep, 1·5±0·9 awake, and 2·1±1·1 during initiated samples ($P=0·02$). In contrast to normal subjects, patients had a significantly higher non-peristaltic background activity ($P=0·002$) which was greater awake than asleep ($P=0·02$). Like normal subjects, the number of peristaltic waves increased significantly in awake periods. but did not further increase with initiated samples.

These findings show that patients with motor disorders have a greater non-peristaltic background activity and an inability to organize oesophageal contractions into peristaltic waves with increasing states of consciousness, suggesting both a central and a peripheral neurological defect Ambulatory manometry is expected to provide a better selection of patients for surgical myotomy by being able to differentiate between psychological and organic motility disorders

Oesophageal dysmotility and its influence on patterns of acid exposure in reflux induced stricture

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Conventional anti-reflux therapy can be highly successful in healing uncomplicated oesophagitis but failures are common once a stricture has developed We have studied patterns of reflux in these two groups to identify a more rational therapeutic approach to reflux stricture

Twenty patients with uncomplicated grade 1–2 oesophagitis (M:F 13:7, age 47 years, range 24–67) and twenty with reflux stricture (M:F 10:10, age 73 years, range 57–87) had a manometric assessment of lower oesophageal sphincter (LOS) pressure and motility characteristics (amplitude of contraction and peristalsis) and 24-h pH monitoring.

	Uncomplicated ($n=20$)	Stricture ($n=20$)	*P* value (χ^2)
Manometry results			
Hypotensive LOS (<6 mmHg)	10 (50%)	8 (40%)	n.s.
>15% simultaneous contractions	0	14 (70%)	<0·001
>50% low amplitude contractions	6 (30%)	14 (70%)	<0·05 (Mann–Whitney)
pH analysis results*			
Upright acid exposure (%)	8·7 (0·3–26·0)	26·4 (0·5–81·7)	<0·05
Supine acid exposure (%)	1·3 (0–14·1)	19·3 (0·1–95·1)	<0·001
Mean duration upright episodes (min)	1·0 (0·4–3·0)	2·0 (0·6–4·8)	<0·01
Mean duration supine episodes (min)	1·0 (0–15·0)	3·0 (1·2–16·2)	<0·001

* Median (ranges)

While LOS pressure is comparable between the two groups, there is significant dysmotility among stricture patients resulting in impaired clearance and prolonged acid exposure These findings explain the different results after total fundoplication between refluxers with or without stricture and support a rationale for evaluation of pro-kinetic drug therapy in the medical management of reflux stricture.

The relationship between gastro-oesophageal reflux and oesophageal motility abnormalities

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Impaired oesophageal motility has been described in patients with gastro-oesophageal reflux (GOR) However, it is unclear whether these abnormalities precede the reflux or are the result of it. Oesophageal manometry was performed in 50 normal subjects and in 56 patients with proven GOR In the patients, 44 per cent of swallows were pathological compared to 16 per cent of those in normal subjects Furthermore, the distal oesophageal contractions were of a lower amplitude ($P<0.01$), but had a similar duration and velocity of propagation. Ten patients who underwent an antireflux repair have returned for postoperative motility studies four show a clear improvement in their motility. This suggests that GOR induces motility changes which are reversible. This clinical observation was tested in 10 cats Reflux was simulated by perfusing the oesophagus with hydrochloric acid (25 mM/l) and pepsin (25 μg/ml) at 1 ml/min for 60 min on 3 successive days Manometry was performed before and one day after the last perfusion. Six cats were then killed and the oesophagus submitted to histology, while four were restudied 3 weeks later without further acid perfusion, and then killed. Perfusion produced mucosal ulceration with or without submucosal inflammation in all cats The immediate post-perfusion manometry showed features similar to those seen in patients, with a reduction in the amplitude of contractions in the distal oesophagus ($P<0.001$), an increase in incidence of pathological swallows ($P=0.01$), but no significant change in wave duration or velocity of propagation. As in postoperative patients these changes were reversible. These clinical and laboratory observations clarify the relationship between GOR and impaired motility and demonstrate their potential reversibility when reflux is prevented.

Manometric assessment of 'pump' function of the oesophageal body

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The squamous-lined oesophagus is protected from damage by refluxed gastric contents by the 'valve' action of the lower oesophageal sphincter and the 'pump' function of the oesophageal body when this mechanism fails. Manometric features related to competence of the cardia have now been identified but pump function of the oesophageal body has only been measured indirectly using clearance of an acid or isotope bolus. This study investigates the manometric pump function of the oesophagus

Forty-eight patients with endoscopic oesophagitis were evaluated using a detailed manometric technique Features associated with poor oesophageal clearance during ambulatory pH monitoring were identified. Twenty asymptomatic volunteers served as controls.

Nine parameters were associated with prolonged clearance of which four were found to be reproducible (*table*)

	Peristaltic amplitude (mmHg)					
	Mean	s.d.	Median	Range	10%	90%
Wet swallows						
Distal 1/3	79·7	32·5	73·5	35–155	42·2	135·8
Middle 1/3	74·0	30·9	66·0	32–160	45·1	129·0
Dry swallows						
Distal 1/3	43·8	17·6	41·3	18–88	21·6	75·5
Middle 1/3	41·9	15·2	44·0	20–68	20·9	66·8

Patients with two or more values below the tenth percentile were considered to have pump failure. Twenty-eight (58 per cent) patients (14 males. 14 females) were found to be abnormal whereas all controls were normal. Reproducibility was assessed in 10 patients after an 8-week interval. Eight of ten were correctly classified on both occasions (6 abnormal, 2 normal)

A new and reproducible technique of directly assessing oesophageal pump function has been developed which may be of value in the preoperative evaluation of patients selected for fundoplication

Gas reflux after fundoplication

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Gas bloat syndrome (GBS) is hypothetically due to an overtight antireflux 'wrap' which prevents belching and results in gaseous stomach distension, postprandial fullness and pain[1] However, there are no supportive data for this hypothesis.

This study has investigated gas reflux after challenge of gaseous distension in nine healthy volunteers and sixteen symptomatic patients after antireflux surgery. GBS symptoms were also evaluated by scored questionnaire Gastric distension was achieved by administration in rapid sequence of 4·5 g sodium bicarbonate and 3·7 g sodium citrate in solution, which liberates 1200 ml CO_2, within 3 min. All belched gas was collected in a closed system and CO_2 concentration and volumes were measured by Rigel CO_2 monitor for 1 h afterwards CO_2 absorption across the gastric mucosa was calculated from the concentration in exhaled air between belches.

CO_2 absorption was identical in volunteers and patients (*table*)

Gas reflux	Total volume belched CO_2 (ml)	P*	Volume per belch (ml)	P*
Volunteers ($n=9$)	435 ± 71	0·05	74 ± 15	0·01
Patients ($n=16$)	324 ± 104		31 ± 7	

Values are mean ± s.e m. *Mann–Whitney *U* test

Symptom score ranged from 0–44 (mean ± s.e.m = 18 ± 3·6) No correlation was observed between symptom score and either total volume of belched CO_2 or volume per belch

The capacity for belching is reduced after antireflux surgery, but this is unrelated to the incidence or severity of GBS symptoms.

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Failed antireflux valvuplasty—when and why

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The Nissen fundoplication is the most widely used surgical therapy for gastro-oesophageal reflux disease However, reflux is not always controlled by the operation. Why this happens has not been adequately documented

Between 1982 and 1987, 101 patients were prospectively studied (median age = 49 years, range 21–74). All were comprehensively investigated both before and after operation, using endoscopy, manometry, and prolonged pH recordings. All underwent Nissen fundoplication for refractory reflux disease Median follow-up was 49 months (range 9–49). Objective postoperative studies were performed at a median of 8 months.

Gastro-oesophageal reflux was controlled in 93 cases (92 per cent). Lower oesophageal sphincter pressure was increased by 4·7 mmHg (median), but there was no correlation between pressure change and reflux control in individual cases.

An intact fundoplication was documented endoscopically in 93 patients In this group reflux was controlled in 92 cases (99 per cent). Eight patients had endoscopic evidence of disruption Reflux was controlled in only one of these cases. Six patients had a second operation at which gross disruption was confirmed Median time to endoscopic recognition of recurrence was 7 months (range 4–10)

Recurrent reflux post fundoplication is due to disruption This can be recognized endoscopically, and occurs during the first postoperative year New approaches to fundoplication fixation may reduce the failure rate.

The manometric features of the lower oesophageal sphincter and oesophageal body, their interaction and relationship to hiatal hernia

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The relationship between competence at the cardia and the function of the oesophageal body in the pathogenesis of reflux oesophagitis is at present unknown. A new manometric technique, based on peristaltic amplitude, has been developed which affords a direct measurement of oesophageal 'pump' function This study investigates the relationship between manometric competence of the cardia, and oesophageal pump function in reflux oesophagitis and their interaction with a hiatal hernia (HH)

Forty-eight patients with endoscopic oesophagitis were evaluated using perfusion manometry. Twenty asymptomatic volunteers served as controls. An incompetent cardia was defined as having one or more of the following features. (1) lower oesophageal sphincter (LOS) pressure $\leqslant 6{\cdot}2$ mmHg. (2) intra-abdominal length $\leqslant 1$ cm. Oesophageal pump failure was diagnosed if patients had 2 or more values for peristaltic amplitude in the distal 2/3 which were below the tenth percentile of the control subjects.

Twelve (25 per cent) patients had normal manometric function Thirty-two (67 per cent) patients had a defective cardia and twenty-eight (58 per cent) had pump failure This was combined in 24 (50 per cent). A HH was combined with a manometric defect in 50 per cent ($n=24$) and was the only abnormality in five (10 per cent) Eighty-five per cent of patients had either a manometric defect or HH

Hiatal hernia occurs as an isolated abnormality in only 10 per cent of patients with reflux oesophagitis Most patients have manometric defect of the cardia, pump or both, frequently co-existing with a hiatal hernia.

Reliable evaluation of the energy status of the remnant liver in hepatectomized patients by measurement of pyruvate/lactate ratio in the arterial blood

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Pyruvate (P), lactate (L), acetoacetate and 3-hydroxybutyrate concentrations (μmol/ml) in the arterial blood were measured enzymatically[1] in each of 20 patients of both sexes who underwent 20–60 per cent hepatectomy for hepatocellular carcinoma or liver metastases before, after liver resection and on the 7th, 14th and 30–35th following days Hepatic energy charge (EC) levels (μmol/g wet tissue) also were assessed at the outset and at the end of hepatectomy by direct measurement of adenine nucleotide concentrations in the liver tissue[1] and calculated according to the formula of Atkinson[2] Mean values $(\times 10^{-2}) \pm$ s.e.m of P/L ratio were $3{\cdot}707 \pm 0{\cdot}450$; $3{\cdot}586 \pm 0{\cdot}085$; $2{\cdot}850 \pm 0{\cdot}685$; $2{\cdot}961 \pm 0{\cdot}410$ and $3{\cdot}584 \pm 0{\cdot}120$. The results were closely and positively correlated ($r=0{\cdot}992$, $P<0{\cdot}01$), with respect to ketone body (KB) ratio (acetoacetate/3-hydroxybutyrate) $0{\cdot}674 \pm 0{\cdot}033$; $0{\cdot}647 \pm 0{\cdot}025$; $0{\cdot}511 \pm 0{\cdot}113$, $0{\cdot}545 \pm 0{\cdot}142$, $0{\cdot}639 \pm 0{\cdot}065$ and with the results of hepatic EC $0{\cdot}841 \pm 0{\cdot}030$; $0{\cdot}807 \pm 0{\cdot}002$ ($r=0{\cdot}999$, $P<0{\cdot}05$). Results therefore suggest that the accurate measurement of P/L ratio in the arterial blood can be regarded as an effective method for evaluating the energy status of the remnant liver in hepatectomized patients (where repeated assessment by direct study of liver tissue is a practical impossibility) and is of importance in helping the surgeon to explain and predict early manifestations of hepatic failure, so that perhaps corrective measures can be taken

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Prevention of hepatic ischaemic damage by aprotinin

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Recently, during hepatic resection, occlusion of the hepatoduodenal ligament was carried out to prevent intra-operative bleeding. In this procedure, the cardinal factor affecting postoperative course is reduction of ischaemic hepatocellular damage, especially in the cirrhotic liver. To assure prolonged viability during this procedure, we examined aprotinin, which possesses cell membrane stabilizing and antiproteolytic effects

The effect on warm ischaemic damage *in vivo* for this experiment we used male Sprague-Dawley rats weighing 220–280 g and 3 h after IV injection of 40 000 units aprotinin, we occluded the afferent hepatic vessels for 60 min and observed the survival rate Saline injected animals served as a control. Of those treated with aprotinin, 11 of 12 animals (92 per cent) survived 60 min warm ischaemia, and among the control animals, only 18 of 32 rats (56 per cent)

Biochemical studies were carried out 12 h after 40 min occlusion of the hepatoduodenal ligament on 6 animals that were treated with aprotinin and also on the 8 saline treated controls

	Aprotinin ($n=6$)	Saline ($n=8$)	P value
GOT	466 ± 71 units/l	641 ± 122 units/l	$<0{\cdot}01$
GPT	376 ± 73 units/l	531 ± 142 units/l	$<0{\cdot}05$

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase

These observations explain the highly protective effect of aprotinin in cases of warm ischaemic damage to the liver

Prolongation of ischaemic tolerance time of the donor liver we used male LEW rats weighing 220–280 g as donor and recipient, and 3 h after IV injection of 40 000 units aprotinin, we perfused the donor liver with chilled Ringer solution (contained 40 000 units/10 ml), preserved 12 h in the cool chamber at 2–4°C and then orthotopically transplanted. The recipient survived more than 4 weeks. Tamaki *et al.*[1] preserved the rat liver for 8 h by using Collins' solution, but only two of seven recipients survived. This shows that premedication of the donor animals with aprotinin has better preservation effects than simple cooling after flushing with Collins' solution.

Aprotinin premedication reduces hepatic damage in both warm and cold ischaemia We suggest that premedication with aprotinin in hepatic resection can be effective for the prevention of hepatic ischaemic damage and that its application in the potential organ donor can also prolong the ischaemic tolerance time of the liver in the transplantation.

Combined effect of thromboxane antagonists and prostacyclin on liver ischaemia *in vivo*

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Thromboxane (Tx), prostacyclin (PGI_2) or their ratio could play an important role in the ischaemic liver injury To study this hypothesis, hepatic vascular occlusion was maintained for 90 min in 6 male Wistar rats, the splanchnic blood being drained through the posterior lobes which are subsequently resected TxB_2 and PGI_2 (measured by RIA after incubation *in vitro* of liver tissues) increase respectively to 302 ± 72 per cent of control ($P<0{\cdot}01$) and 167 ± 18 per cent ($P<0{\cdot}01$) after 90 min of ischaemia and to 482 ± 171 per cent ($P<0{\cdot}05$) and 243 ± 45 per cent ($P<0{\cdot}01$) after 30 min of revascularization. In order to examine if these changes could influence the survival rate (SR) of animals submitted to the same period of ischaemia, drugs were used to decrease the relative importance of Tx over PGI_2. The SR of untreated rats (17 per cent 3/18) is not modified by IV administration of 3·6 μg/kg PGI_2 (2/6) In contrast, imidazole (12·5 mg/kg), an inhibitor of Tx synthesis, significantly increases the SR to 67 per cent (12/18, $P=0{\cdot}006$) With this drug the PGI_2 production should increase, to elucidate this possible interference, an antagonist of Tx was used. Daltroban 1 mg/kg improves the SR (6/12) but not significantly unless supplemented with PGI_2 (3·6 μg/kg), in this case the results are the same as with imidazole (67 per cent, 8/12, $P=0{\cdot}006$)

These results can thus be interpreted in terms of balance of actions between Tx and PGI_2 After ischaemia their ratio increases to such a level that addition of exogenous PGI_2 could be ineffective unless the influence of Tx is decreased. A simultaneous reduction of Tx concentration or action and an increase of PGI_2 seems to be needed to obtain the greatest impact on the survival rate

Can thromboelastography detect coagulopathy associated with liver ischaemia?

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Major haemorrhage occurs during hepatic transplantation and resection (with or without hilar clamping), due, in part, to the coagulopathy associated with liver ischaemia Thromboelastography (TEG) has been advocated as a rapid and sensitive method for determining the intra-operative correction of such coagulopathies[1]

To test this nine male pigs were subjected to 2 h warm liver ischaemia followed by 2 h hepatic reperfusion Blood was taken from a CVP line for TEG and conventional tests (PT, PTT and platelet count). The circulation was maintained during the ischaemic period by shunting the ortal vein and inferior vena cava to the internal jugular vein, using a ocal prostacyclin infusion to prevent the shunt clotting[2]

esults	Pre-ischaemia	2 h ischaemia	1 h reperfusion	2 h reperfusion
T	9·8 (1·8)	9·4 (0·4)	11·4 (0·6)	11·1 (0·8)
TT	17·0 (1·1)	17·9 (1·0)	24·6 (1·3)‡	22·9 (1·6)*
latelet count	523·4 (48·7)	441·0 (37·4)*	382·9 (40·8)*	351·2 (26·2)*
EG 'r'	12·4 (1·1)	10·1 (1·0)	17·8 (1·1)§	17·7 (1·1)*
EG 'k'	4·4 (0·5)	4·4 (0·4)	10·5 (1·3)†	10·1 (1·2)†
EG 'Ma'	63·8 (3·2)	62·6 (2·1)	51·7 (2·7)§	52·2 (2·8)§
EG 'Raby index'	56·3 (10·4)	44·2 (7·9)	14·2 (3·1)†	14·1 (2·0)†

alues are mean ± s.e.m. Analysis for a paired *t* test; $^*P<0·05$; $P<0·01$; $^‡P<0·001$; $^§P<0·0001$. PT, prothrombin time, PTT, partial hromboplastin time. TEG parameters listed in the table are standard arameters[3]

There was little change in coagulation during 2 h liver vascular ypass. Hypocoagulation occurred following reperfusion indicated by ises in PTT and PT. The changes in TEG parameters were more obvious, obtained more rapidly and indicated specific clotting defects which can be used to guide replacement therapy

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Different renal handling of electrolytes following portocaval shunt in the normal and cirrhotic rat

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Renal function may be seriously impaired in liver disease. This study was therefore initiated to elucidate renal handling of vital electrolytes following portocaval shunt in normal and cirrhotic rats. Male Sprague-Dawley rats were assigned to the following groups: normal rats and cirrhotic rats[1]. In each group either a sham operation or a portocaval anastomosis (PC) was performed. One week postoperatively a 24 h urinary collection period followed, thereafter blood was collected via the abdominal aorta. Calculations: glomerular filtration rate (GFR; ml/min), fractional excretion (FE; per cent) of electrolytes

	Normal		Cirrhotic	
	Sham	PC	Sham	PC
GFR	0·64 ± 0·11	1·92* ± 0·69	0·78 ± 0·20	0·96 ± 0·11
FE_a	0·63 ± 0·11	0·34* ± 0·08	0·18 ± 0·04	0·31* ± 0·08
FE_K	40·6 ± 4·25	22·6* ± 3·03	20·0 ± 3·81	16·4 ± 3·06
FE_{ca}	0·20 ± 0·04	0·35* ± 0·10	0·09 ± 0·04	0·11 ± 0·03

Values are mean ± s.e.m. $n=8$; $^*P<0·01$, Student's *t* test

PC induces major changes in renal electrolyte handling in the normal rat, whereas in the cirrhotic rat PC has only minor effects.

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Role of the arachidonic acid cascade in liver integrity

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Restoration of liver integrity after parenchymal damage or surgical resection depends on various stimulatory factors. The first stimulating factor concerned seems to be related to prostaglandin, as exogenous PGE_2 induces equal transmembrane ion fluxes or hepatocellular hyperpolarization (ΔMP) as recorded after 70 per cent liver resection (PH).

The aim of this study was to test *in vivo* the correlation between arachidonic acid cascade (AAC), ΔMP and liver regeneration by interfering at different levels of the AAC before and after PH either at the level of its synthesis or its mobilization. AAC synthesis (phospholipase dependent) was inhibited by intravenous (IV) or intramuscular (IM) dexamethasone administration (0·2 mg/100 mg) 30 min before PH ($n=19$), ACC mobilization (cyclo-oxygenase dependent) was prevented by intraperitoneal (IP) or oral (O) indomethacin (6 mg/100 mg) given respectively 4 h or 24, 16 and 8 h before PH ($n=9$). All series were compared with sham treated animals ($n=18$).

Membrane potential was recorded by repeated micro-electrode cell puncture before and at different times during the first 24 h which followed PH. Liver regeneration was assessed by [^{3}H] thymidine incorporation 24 h after PH. Depending on the doses and length of treatment with AAC inhibitory drugs, ΔMP fell from 6·9 ± 0·8 mV to 1·8 ± 1·1 mV 15 min after PH with dexamethazone treatment ($P<0·005$) or from 7·3 ± 0·7 mV to 1·1 ± 0·6 mV 18 h after PH with indomethacin treatment ($P<0·005$).

Absence of post PH ΔMP was directly correlated with inhibition of the liver regeneration which fell both after dexamethazone and indomethacin treatment from 15 620 ± 3100 d.p.m./mg DNA to (IV) 2150 ± 420, (IM) 2010 ± 300, (IP) 3200 ± 1700 and (O) 2019 ± 590 d.p.m./mg DNA ($P<0·05$)

For the first time we have shown that both membrane hyperpolarization and normal liver regeneration can be blocked by prolonged inhibition of the arachidonic acid cascade which could have direct clinical implications in cases of acute hepatitis or liver resection.

The value of intra-operative ultrasonography and ultrasonic dissection in liver surgery

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Performing liver resections for various hepatobiliary diseases has a considerable morbidity and mortality. The aim of our study was to evaluate whether intra-operative ultrasound and ultrasonic liver parenchyma dissection were able to lower the incidence of complications and associated mortality. Therefore we analysed the reports of patients who underwent a liver resection in the period from January 1972 to May 1987. In this period 95 partial liver resections were performed; 44 for benign diseases, 35 for malignancies and 16 for traumatic liver diseases. Resections were classified as 'major' if they were right or left lobectomy or trisegmentectomy. The other resections were considered to be 'minor'. Small wedge resections were not included in this study. Of the 79 patients with non-traumatic diseases, 25 were operated on with the use of intra-operative ultrasound and ultrasonic liver parenchyma dissection. Comparing these 25 patients with the 54 patients who were operated on without these techniques we could not find any difference in age, sex ratio, underlying disease and number of major *versus* minor resections. The number of complications was lower in the group operated with intra-operative ultrasound and ultrasonic dissection. Considering the major resections only there was a decrease in complication rate from 65 per cent (without adjunctive techniques) to 29 per cent (with adjunctive techniques). The amount of blood loss tended to be lower in the group operated on with adjunctive techniques. The disadvantage of a longer operation time in resections with adjunctive techniques compared with resections without these techniques (this difference was statistically significant in the major resection group) did not lead to a higher complication rate

From this retrospective clinical study we conclude that intra-operative ultrasound and ultrasonic liver dissection are useful techniques in lowering the incidence of postoperative complications and associated mortality

Liver transplantation may cure primary biliary cirrhosis

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Deteriorating liver function in primary biliary cirrhosis (PBC) remains one of the prime indications for hepatic replacement but controversy exists as to whether PBC can recur in the grafted liver[1–4]. Twenty-three patients surviving longer than 3 months (range 4 months–5½ years), including 17 surviving longer than one year, who received orthotopic liver grafts to treat PBC underwent detailed clinical, biochemical, immunological and histological studies.

No clinical syndromes associated with PBC have been encountered. Nineteen (83 per cent) of the patients currently have normal biochemical liver function (LFT), with LFT abnormalities proved to be due to biliary drainage problems in three and to chronic rejection in one. All patients had positive antimitochondrial antibody (AMA) (titres 40–1600) before transplantation and 18 (78 per cent) showed a reduction in AMA titre after transplantation of which 14 (61 per cent) have subsequently risen. Of the 15 known to have elevated IgM pretransplantation, all levels fell after grafting but 17 (74 per cent) of the 23 currently have elevated levels of IgM. Liver biopsies from 14 of the 1 year survivors (range 1–5 years) were examined 'blindly' along with biopsies from 8 other patients grafted for equal lengths of time for different diseases. Both groups showed mild portal inflammatory changes. None of the PBC group had any specific histological features to suggest recurrence of PBC in the new liver.

While immunological markers of PBC remain after grafting in patients transplanted for PBC we cannot detect clinical, biochemical or histological evidence to support the hypothesis that PBC recurs after transplantation.

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Local recurrence after pre-operative radiotherapy and surgery in rectal cancer

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Radiotherapy is being increasingly used as an adjunct to surgery in rectal cancer. The response to radiotherapy is not uniform and it is desirable to develop indicators to predict response. The present study involves 186 patients with tethered rectal cancer, who were randomized into two groups, 97 patients had surgery alone and 89 had pre-operative radiotherapy (20 Gy in 4 fractions). The DNA ploidy status was determined by flow cytometry in all patients.

DNA aneuploidy was detected in the resected tumours of 60 (62 per cent) in the surgery only group, but in only 33 (37 per cent) after radiotherapy ($\chi^2 = 10{\cdot}42$, $P < 0{\cdot}01$).

There was a significant reduction in local recurrence after radiotherapy (log rank, $P < 0{\cdot}0001$). DNA diploid tumours were less likely to recur locally than DNA aneuploid tumours. This was more marked in the radiotherapy group ($P = 0{\cdot}003$) than the surgery only group ($P = 0{\cdot}03$). In multivariate regression analysis of the patients who had radiotherapy, DNA ploidy is an independent predictor of local recurrence while Dukes' stage is not.

DNA ploidy may indicate response to radiotherapy and is an important predictor of subsequent local tumour progression.

Regulation of proliferation of breast cancer cells by growth factors

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Recent studies have indicated that oestrogenic control of proliferation of receptor positive (ER +ve) breast cancer cells *in vitro* may be mediated by stimulatory and inhibitory autocrine growth factors.

The aim of this study was to examine the expression of oestrogen receptors (ER) and transforming growth factor β(TGF-β) in the ER +ve breast cancer cell line ZR-75 during and after α-interferon (α-IF) induced cytostasis.

ZR-75 cells were exposed continuously to α-IF (500 IU/ml) for up to 10 days and were harvested at intervals for estimation of cell number, extraction of RNA and measurement of ER (by radioligand binding). RNA was bound to nitrocellulose membranes and prepared for autoradiography following hybridization to ^{32}P-labelled cDNA probes for TGF-β and ER. Cell surface TGF-β receptors were measured by a radioligand method. Control cultures without α-IF were examined in the same way.

α-Interferon has a significant antiproliferative effect (cell doubling time, control (36 ± 8 h) *versus* α-IF treated (126 ± 27 h, $P < 0{\cdot}001$). It also reduced ER concentrations to 30 per cent of control values, with a parallel fall in ER mRNA. TGF-β mRNA levels were increased 5–10-fold in response to α-IF. Cytostasis and mRNA effects were maintained until α-IF was removed from the medium, at which point the cells started to regrow and mRNA levels (ER + TGF-β) returned to normal within 24 h. High affinity TGF-β receptors were demonstrated (5800 sites per cell, Kd = 70 pM) and co-treatment with a blocking anti-TGF-β antibody reduced the antiproliferative effect of α-IF by 60 per cent.

These results suggest that the cytostatic effect of α-IF in this cell line is mediated by TGF-β autoinhibition of cell growth.

The relationship between pancreatic duct pressure, duct permeability and acute pancreatitis

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Perfusion of activated pancreatic enzymes along the feline pancreatic duct, made permeable by glycodeoxycholate perfusion or oral alcohol administration, results in acute pancreatitis[1,2]. Increased pancreatic duct pressure (PDP) may also be implicated in pancreatitis. We studied the effects of 15 mM glycodeoxycholate perfusion (0·5 ml/h) (group 2), intragastric alcohol (20 ml 40 per cent) (group 4) and secretin stimulated pancreatic secretion against duct obstruction (SS/O) of > 50 per cent (group 6), in cats, on PDP, ductal permeability and the development of pancreatitis. Control animals received duct perfusion with saline (group 1), intragastric saline (group 3) or SS/O of < 50 per cent (group 5). In all groups PDP was measured continuously for 1 h. Ductal permeability was assessed by recovery of 20 000 molecular weight dextrans in portal blood following their ductal perfusion. Then the duct was perfused with activated pancreatic enzymes for 1 h and the pancreas assessed histologically for pancreatitis at 24 h. In groups 2, 4 and 6 PDP and duct permeability were increased and pancreatitis resulted in most animals. These effects were not seen in control groups 1, 3 and 5.

Group (*n*)	1 (6)	2 (6)	3 (6)	4 (6)	5 (10)	6 (17)
PDP (±s.e.m.)	8·7	22·1	8·7	14·5	12·8	23·2
(mmHg)	±0·6	±4·7*	±0·4	±1·3*	±2·0	±1·7*
Permeability	0/6	5/6†	0/6	5/6†	2/10	12/17†
Pancreatitis	0/6	6/6†	1/6	6/6†	2/10	12/17†

$P < 0{\cdot}05$ *versus* controls (*Mann–Whitney and †Fisher's tests)

Increased PDP resulted in increased ductal permeability to macromolecules. These changes may be important initiating events in acute pancreatitis.

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Does conservation therapy for breast cancer reduce psychological morbidity?

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There is an appreciable incidence of psychological morbidity associated with mastectomy[1]. This has encouraged a trend towards conservation therapy for early breast cancer, although the psychological benefit of less mutilating surgery is unproven.

The aim of this study was to assess the psychological state in patients undergoing surgery for benign and malignant breast lumps.

A previously validated self-administered questionnaire[2] was completed pre-operatively and 1 year postoperatively by 243 patients

The table shows the number of individuals exceeding pre-determined thresholds for psychological morbidity

		Anxiety	Depression	Sexual problems
Benign	Pre-operative	40 (38%)	27 (26%)	22 (21%)
$n=105$	Postoperative	19 (18%)	15 (14%)	22 (21%)
Conservation treatment	Pre-operative	31 (50%)	20 (32%)	16 (26%)
$n=62$	Postoperative	16 (26%)	16 (26%)	20 (32%)
Mastectomy	Pre-operative	41 (54%)	25 (33%)	27 (36%)
$n=76$	Postoperative	23 (30%)	14 (18%)	22 (29%)

The incidence of psychological morbidity was not significantly different when the three patient groups were compared pre-operatively or at 1 year after surgery.

No association was found between psychological morbidity and age or adjuvant therapy

The results indicate that conservation therapy is not associated with less morbidity than mastectomy for anxiety, depression and sexual problems at 1 year follow up.

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Delayed gastric emptying does not contribute to gastro-oesophageal reflux disease

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Seventy-six patients with symptoms of heartburn and/or regurgitation and 38 asymptomatic volunteers were studied with 24 h pH oesophageal monitoring, gastric emptying of ^{99m}Tc labelled oatmeal and oesophageal manometry. Endoscopy was performed on all patients and the degree of oesophagitis was graded. Sixty-seven per cent of the symptomatic patients had increased exposure of the oesophagus to gastric juice As expected, these patients, when compared with those without acid reflux and controls, had a shorter overall length of the LES ($2\cdot7\pm1\cdot0$ *versus* $3\cdot4\pm1\cdot0$ cm, $P<0\cdot01$), shorter abdominal length of the LES ($1\cdot1\pm0\cdot7$ *versus* $1\cdot8\pm0\cdot9$ or $2\cdot2\pm0\cdot7$ cm, $P<0\cdot01$) with a lower pressure ($8\cdot6\pm5\cdot2$ *versus* $11\cdot3\pm5\cdot9$ or $14\cdot2\pm5\cdot1$ mmHg, $P>0\cdot06$) and more oesophagitis (63 *versus* 12 or 1 per cent, $P<0\cdot001$). Delayed gastric emptying occurred as frequently in patients with reflux as in those without reflux (37 per cent *versus* 44 per cent of patients) There was no association between delayed gastric emptying and poor LES function and there was no evidence that delayed gastric emptying was the cause of reflux in patients with normal LES function. Oesophagitis, a complication of reflux disease, was not associated with delayed gastric emptying in patients with proven reflux On the contrary, patients with delayed gastric emptying had less oesophagitis ($P<0\cdot05$). This suggests that the prolonged presence of food in the stomach may have a buffering capacity on gastric acidity. We conclude that, contrary to popular opinion, delayed gastric emptying is not a major factor in the pathophysiology of gastro-oesophageal reflux disease and that therapy aimed at speeding gastric emptying cannot be supported by the results of this study.

Regulation of hepatic regeneration by interleukin-2-activated killer cells and effect of cyclosporin A

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We have investigated the implication of interleukin-2 (IL-2) and the effect of cyclosporin A (CsA) on hepatic regeneration after standard 70 per cent partial hepatectomy (HEP) in C3H/He mice. Hepatic regeneration was assessed by measurement of ^{3}H-TdR incorporation into regenerating hepatocytes and of frequency of BrdU positive hepatocytes in the regenerating liver Cytotoxic activity of lymphocytes was determined in a ^{51}Cr release assay. HEP enhanced spontaneous and Con A-induced IL-2 production in spleen cells. Spleen cells and hepatic non-parenchymal lymphocytes from HEP mice had cytotoxic activity against regenerating hepatoblast, and cytotoxicity of these cells was more augmented by culture with recombinant IL-2 (rIL-2) for 4 days or by administration of exogenous rIL-2 than that of cells from control laparotomy mice. Hepatic regeneration was significantly inhibited by administration of exogenous rIL-2 as well as by adoptive transfer of rIL-2 activated HEP spleen cells. *In vivo* administration of CsA, an inhibitor of IL-2 production, significantly enhanced hepatic regeneration after HEP. Neither rIL-2 nor CsA had direct effects on growth of cultured regenerating hepatoblasts in the dose studied These results suggest that the hepatic regeneration after HEP is regulated by IL-2-activated killer cells induced by endogenous IL-2 production after HEP.

Sepsis and anaerobic metabolism: effects on mitochrondrial activity

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The accelerated anaerobic metabolism (blood lactate >5 mM/l) often seen in sepsis is thought to occur from deactivation of the TCA cycle ('coarse control'). To test this hypothesis, nine non-septic (group 1) and nine septic patients (group 2 and group 3) had skeletal muscle mitochondria isolated and assayed to determine. respiratory activity (RCI—a ratio of state 3:state 4 activity); and the activity of pyruvate and the TCA intermediates malate (M), α-ketoglutarate (K) and oxaloacetate (O) in relation to the absence (group 2) or presence (group 3) of accelerated anaerobic metabolism.

	Groups			ANOVA		*t* statistic	
	1	2	3	F	*P*	$u_1=u_3$	$u_2=u_3$
Lactate	1·47±0·72	1·27±0·48	6·69±4·45	7·75	0·01	0·01	0·025
Pyruvate	0·08±0·05	0·08±0·04	0·28±0·07	17·7	0·01	0·001	0·001
RCI	4·55±0·72	3·75±1·12	4·42±0·85	1·04	n s	n s	n s
O	0·83±0·24	1·63±1·45	0·52±0·30	2·38	n s	n s.	n s
K	1·97±1·47	0·85±0·48	1·09±0·54	1·25	n s	n s	n.s
Malate	3·80±1·28	4·46±0·84	1·58±0·85	7·56	0·01	0·025	0·025

Analysis of variance (ANOVA)—the null hypothesis ($u_1=u_2-u_3$) was tested against the alternative. A significant F test ($P<0\cdot05$) rejects the null hypothesis and identifies comparisons of interest. These were analysed by the two sample *t* test utilizing the Bonferroni procedure [t(0·05/3/2)]. These findings suggest that· sepsis, even in the presence of accelerated anaerobic metabolism, does not impair the ability of skeletal muscle mitochondria to utilize O_2 and substrate *in vitro*: and during anaerobic metabolism normal entrance into the TCA cycle is blocked with oxaloacetate activity maintained at the expense of malate (malate shuttle system), findings not characteristic of coarse control.

Urgent cardiac transplantation—a prospective study

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Cardiac transplantation is now a widely accepted procedure in patients with severe uncontrolled cardiac insufficiency. Indication for urgent transplantation in critically ill acute patients remains however controversial, mainly because of a relative shortage of donor hearts.

Evaluation of the operative risk in acute patients has been carried out prospectively, in a group of 50 cardiac transplant candidates from 1982 to 1988 Group A ($n=17$) included acute indications, on urgent patients, maintained in ICU alive either by IV pharmacological treatment, or/and by mechanical systems for temporary circulatory support, ECCMO or Jarvik total heart ($n=3$). Group B ($n=16$) included patients waiting for transplant at the hospital. Group C ($n=17$) were regular priority patients waiting at home. The policy for selection of the priority was to consider group A as a maximal priority. Immunosuppressive regimen was identical in each group, including cyclosporin, steroids, ATG, azathioprine The 3 months mortality rate was respectively 53 per cent in group A, 13 per cent in group B, 6 per cent in group C The cause of death in group A was related to septic complications in 44 per cent The complete rehabilitation rate was 41 per cent in group A, 69 per cent in group B, 71 per cent in group C.

This experience should lead to a more accurate selection of the recipients and to question the highest priority for a donor heart given to an acute patient

Cholelitholysis: a comparison of gallstone dissolution solvents

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The development of the extracorporeal shockwave lithotripsy (ESWL) as a non-operative treatment of gallbladder stones requires an adjuvant therapy to eliminate the residual fragments after ESWL. Therefore, the use of solvents for direct percutaneous gallbladder perfusion will be of renewed interest To dissolve cholesterol stones in the biliary tract monoctanoin (MO) was of limited use Recently, new solvents, such as methyl ter-butyl ether (MTBE) and D-limonene preparations have become available We compared under identical conditions the solubilizing capacity *in vitro* of (1) MTBE, (2) MO, (3) LIM (97 per cent D-limonene with 3 per cent surfactants added) and (4) LIM/MO (70 per cent/30 per cent).

Sets of four gallstones from ten different patients, median weight 460 mg (range 29–2046), were immersed individually in tubes containing one of the four solvents at 37°C. Stones were weighed at fixed intervals and chemical analysis of one stone of each set was carried out

Two of the ten stones were pigment stones without cholesterol, they disintegrated into fragments without complete dissolution The other eight stones contained >90 per cent cholesterol and seven dissolved completely, often leaving sandlike debris

Weight reduction	MTBE	MO	LIM	LIM/MO
25%	10	1340	71*†	56*
50%	26	2753	226*‡	135*

Each value represents median dissolving time (min) for 8 stones (>90 per cent cholesterol)
**versus* MTBE: $P<0\cdot01$
† *versus* LIM/MO n s
‡ *versus* LIM/MO $P<0\cdot05$

In vitro MTBE dissolves human cholesterol gallstones approximately five times faster than LIM/MO, while LIM/MO is more effective than LIM alone. However, MTBE was less effective for pigment stone than for cholesterol stone dissolution As efficacy of MTBE is superior, further evaluation of MTBE to dissolve residual fragments after ESWL treatment is warranted

Current selection criteria of gallstone patients for extracorporeal shock wave lithotripsy are no longer valid

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Extracorporeal shock wave lithotripsy (ESWL) is successful in fragmenting gallstones but <10 per cent of patients fulfil the criteria considered suitable for treatment, i e radiolucent stones fewer than three in number and <3 cm in diameter[1]. However, no data exist to substantiate current selection criteria In this study, employing a second generation EDAP lithotripter, 37 patients with gallstones have received treatment. Of these, only four satisfied the previously accepted selection criteria The remaining 33 patients either had stones >3 cm in size, were more than 3 in number or were radio-opaque. All patients received up to five sessions of ESWL (6000 shock waves per session) without sedation. Early results have demonstrated complete gallstone clearance in five patients (mean treatment sessions 3·5) and >50 per cent clearance in 12 patients (mean number of treatments 3·7) still undergoing therapy Of those patients with a successful outcome only four would have satisfied traditional selection criteria There was no mortality. One patient developed biliary colic following ESWL. W conclude from this ongoing data that the previously accepted selectio criteria for ESWL greatly underestimates the number of suitabl patients and that technical advances in ESWL may have widened th scope of this therapy.

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Defining parameters for common duct laser lithotripsy.

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Endoscopic laser lithotripsy offers a potential means of fragmenting biliary stones that are impacted in the lower end of the common bile duct in the 10 per cent of patients in whom ERCP and sphincterotomy have failed This paper explores the absorption spectrum of bile, relating this to the most efficient laser wavelength for gallstone fragmentation Quantitative spectrophotometry was used to analyse the absorption of six samples of human bile. All samples had an absorption peak at 420 nm falling to a minimum at 1100 nm Calculi of similar size but varying appearance, from six patients with multiple stones, were divided into four groups and exposed to pulsed laser energy at wavelengths of 440, 480, 500 or 560 nm. Energy was transmitted by a 320 μm diameter flexible optical fibre, held in contact with the stone by a counterbalanced arm

Mean fragmentation energies *versus* wavelength

Wavelength (nm)	440	480	500	560
Energy (J)	4·6±2·6	6·9±3·9	11·9±5·0	14·3±6·5

The energy threshold for stone surface damage at each of the four laser wavelengths tested was similar, but the fragmentation energies were significantly smaller at 440 nm compared with 500 nm ($P<0\cdot05$) and 560 nm ($P<0\cdot01$) (Mann–Whitney *U* test). Stone fragmentation is most efficient with the pulsed dye laser wavelength of 440 nm and occurs only when the delivery fibre is in contact with the stone. In clinical practice the absorption spectrum of bile would allow stray laser light at 440 nm to be strongly absorbed, thus minimizing the risk of bile duct damage.

The pancreatic duct occlusion with fibrin sealant (FS) following pancreatic head resection for the protection of the pancreatico-digestive anastomosis

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A dehiscence of the pancreatico-digestive anastomosis occurs even when a healthy lienal pancreas segment following pancreas head resection due to carcinomas must be anastomosed with the intestinal tract (incidence 5–35 per cent) A reduction of postoperative complications could be achieved by pancreatic duct occlusion (PDO) with prolamin because a quick irreversible exocrine insufficiency results, but there is still controversy concerning the possibility of endocrine damage with this method.

Therefore, the goal of our experimental study in domestic piglets was to block the exocrine secretion only temporarily by PDO with fibrin sealant (FS) to ensure a safe protection of the anastomosis. Our long-term studies up to 6 months postoperatively with PDO with FS showed that a high local concentration of aprotinin of 20 000 IU/ml is necessary to blockade the exocrine secretion for the first 5 postoperative days. Contrary to PDO with prolamin there have been no morphological and functional sequences for the lienal pancreas.

PDO with FS resulted in a temporary rise of the amylase levels and a low-grade interstitial fibrosis However, the exocrine and endocrine pancreas tissue and functions were conserved. The healing of the pancreatico-digestive anastomosis was undisturbed.

This new method for the protection of the pancreatico-digestive anastomosis has already been performed successfully in 11 patients who underwent partial duodenopancreatectomies owing to carcinomas. During the observation period of up to 16 months we saw no damage of the exocrine and endocrine functions

Are common bile duct (CBD) stones important in acute gallstone pancreatitis

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The relationship between common bile duct (CBD) stones and actual outcome in acute pancreatitis due to gallstones (AGP) is not known.

One hundred patients with AGP had endoscopic retrograde cholangiopancreatography (ERCP) during the same admission and this was successful in 94 cases. Thirty-eight patients had predicted severe (PS) attacks and sixty-two were predicted mild (PM, modified Glasgow criteria). The incidence of CBD stones is shown in the *table*. The incidence of complications due to pancreatitis was 35 per cent in patients with PS attacks *with* CBD stones, 29 per cent in PM attacks *with* CBD stones, 22 per cent in PS attacks *without* CBD stones and 7 per cent in PM attacks *without* CBD stones ($\chi^2=9{\cdot}9$, df 3, $P<0{\cdot}05$, complications in all patients with CBD stones *versus* no CBD stones, $\chi^2=6{\cdot}89$, df 1, $P=0{\cdot}0088$) Endoscopic sphincterotomy (ES) was performed in the 37 patients with CBD stones (no deaths), the overall mortality was only 2 per cent.

Time of ERCP	PS	PM	χ^2	d.f	P
<72 h	14/23 (61%)	9/26 (35%)	8·43	3	<0·05
3–30 days	6/12 (50%)	8/33 (24%)			
All cases	20/35 (57%)	17/59 (29%)	7·39	1	<0·007

These original findings show an important relationship between predicted outcome, CBD stones and actual outcome; ERCP ± ES can contribute to a low mortality, and should be more widely adopted.

Successful chemical 'cholecystectomy' in the pig

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The methods currently available for the non-surgical treatment of gallstones do not prevent recurrence after their dissolution/fragmentation[1] A series of experiments in pigs was designed to achieve safe chemical destruction of the gallbladder mucosa as an alternative to surgical removal.

After the establishment of an access cholecystostomy, performed under laparoscopic control, the tract is dilated to enable introduction of a choledochoscope into the gallbladder A balloon-tipped catheter is inserted into the cystic duct to block its lumen. Na_2CO_3, 30 per cent which has a low LD_{50} was used with a contact time of 10 min followed by saline washing of the gallbladder Progress of the lesion was followed by serial tube cholecystocholangiograms until the pigs were killed 3–4 months later.

The first three animals died (rupture of CBD due to over-inflation of cystic duct balloon, leakage of Na_2CO_3 into the biliary tract, $n=2$). The technique was modified to ensure cystic duct obstruction and the ensuing seven pigs remained well until their deaths The serial contrast studies showed progressive shrinkage of the gallbladder lumen with obliteration at 6–10 weeks and a normal/patent biliary tree. The histology at post mortem showed complete transmural fibrosis of the gallbladder with a normal biliary tract and liver parenchyma

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Anal carcinoma—patient prognosis and flow cytometric DNA analysis

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Using flow cytometric DNA analysis of paraffin embedded tissue, DNA histograms were successfully obtained from the anal cancers of 117 patients. DNA diploid patterns were given by 82 cancers (70 per cent and DNA non-diploid patterns by 35 cancers (30 per cent)—15 DNA aneuploid, 20 DNA tetraploid Well-differentiated squamous cell cancers were mainly (81 per cent) DNA diploid, while a larger proportion of poorly differentiated (30 per cent) and small cell cancers (40 per cent) were DNA non-diploid. The large majority of stage A cancers (86 per cent) were DNA diploid. A greater proportion of tumours that had invaded through the anal sphincter (35 per cent) or had lymph node metastasis (30 per cent) or distant spread (50 per cent) were DNA non-diploid.

Prognosis was poorer for patients with DNA non-diploid tumours (52 per cent alive at 5 years) when compared with patients with DNA diploid tumours (66 per cent alive at 5 years) ($P=0{\cdot}08$); and significantly poorer for individuals with DNA aneuploid anal cancers (43 per cent alive at 5 years) ($P=0{\cdot}037$) However, in a multivariate analysis model, the DNA ploidy pattern of an anal cancer was not of independent prognostic significance alongside tumour histology and tumour stage.

Extent of sialomucin predicts patients at risk of local recurrence of colorectal cancer

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We have observed that a sialomucin band extending 3 cm or more from colorectal cancer is associated with tumour penetration into adjacent structures This study has evaluated whether the presence of sialomucin at 3 cm or more from the tumour is associated with increased risk of local recurrence

The presence of sialomucin was estimated by high iron diamine–alcian blue stain in 256 patients undergoing 'curative' colorectal carcinoma excision with distal resection margin of at least 3 cm. Patients were evaluated for local recurrence for a median of 24 months from operation by routine clinical examination and sigmoidoscopy, and where appropriate, ultrasound CT scan and colonoscopy

Sialomucin was present at 3 cm or more from the tumour edge in 75 (29·2 per cent) patients. Local recurrence occurred significantly ($\chi^2=7{\cdot}12$, $P<0{\cdot}01$) more often in this group (29·3 per cent) than among patients in whom a 3 cm sialomucin band was absent (14·9 per cent)

Multivariate analysis demonstrated that in addition to Dukes' stage and hospital of operation, a sialomucin band of >3 cm from the tumour was an independent predictor of local recurrence ($P<0{\cdot}007$).

Pre-operative biopsy for sialomucin adjacent at 3 cm from primary tumour appears to indicate patients at greater risk of local recurrence

Evidence against the role of chromosomes 17p and 5q in early colorectal carcinogenesis

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Recent work has shown that inactivation on both chromosomes of certain genes can be carcinogenic[1]. A common way for these anti-cancer genes to be damaged is through chromosomal deletion, this can sometimes be detected as loss of heterozygosity at the appropriate loci. Loss of heterozygosity has been observed in sporadic colorectal cancers at loci on 5q [2] and 17p [3] As colorectal cancer is believed to originate in adenomas, it is important to see if these loci are homozygous in the precancerous condition Of 35 adenomas examined at 17p, only one showed chromosomal loss[3], and in 14 adenomas examined at 5q, all were heterozygous[2,4]. However, in only two cases have both loci been examined in the same sample[4], and histological classification reported for only three samples[3]. We have looked at 15 adenomas obtained at colonoscopy; one half of each polyp was sent for histology and the remaining half was examined using probes for loci on 17p and 5q Peripheral leucocytes were used as a source of control tissue. The probes used recognize multi-allelic loci and heterozygosity was found in 10 out of 15 samples at 5q and 12 out of 15 samples at 17p In no case was there a reduction to homozygosity in the adenomas, even though histological grading showed a wide range of abnormalities in the different samples. These data suggest that the probability of homozygous loss at either of the loci examined being associated with the early stages of carcinogenesis is highly unlikely

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The use of *in situ* hybridization to demonstrate the intranuclear and morphological distribution of HPV 16 DNA in anal cancer

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The evidence for an aetiological association between HPV 16 and squamous cell carcinoma of the anus, using membrane hybridization has been presented to this society previously[1] Southern blot analysis can distinguish between incorporation of viral DNA into the host genome and episomal (unincorporated) DNA within cells, but cannot demonstrate that any of this DNA is within the neoplastic epithelial cells rather than within stomal cells. *In situ* hybridization provides this information.

Using this technique we have detected HPV 16 DNA within the nuclei of malignant cells in 16 of 32 anal squamous cell carcinomas. We were able to demonstrate HPV 16 DNA in the same 16 plus another 2 by membrane hybridization using Southern blot analysis The two cases in which *in situ* and membrane hybridization differed were those in which Southern blot analysis had shown there to be a low copy number (< 10 copies per cell).

In situ hybridization is a useful technique with potential uses in providing a method for the detection of viral and cellular oncogenes in fixed tissue We have shown that it can provide similar sensitivities to Southern blot analysis.

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A prospective evaluation of the influence of tumour cell DNA content on recurrence in colorectal cancer

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Tumour cell DNA content (ploidy) has been shown retrospectively to have a significant influence on survival in colorectal cancer We measured ploidy prospectively in 251 consecutive patients, who had resections for colorectal cancer and have been followed for a median of 3 years (1–5 years), to assess the influence on recurrence

DNA content was measured by flow cytometry on tumour cells derived from freshly resected specimens and paraffin blocks. All local and distant recurrence was carefully investigated and recorded In all 139 (55 per cent) tumours contained cells with abnormal DNA content (aneuploid or tetraploid) A slightly greater proportion of abnormal DNA tumours (38/139, 27 per cent) were pathological stage C compared with diploid tumours (22/112, 22 per cent). Results of the patients who had potentially curative surgery are shown in the *table*.

Pathological stage	Local and distant recurrence		
	Diploid	Aneuploid	Tetraploid
A	1/21 (5%)	3/14 (21%)	0/3
B curative	5/49 (10%)	16/49 (33%)	0/5
C curative	9/18 (50%)	15/33 (45%)	1/3

Patients with stage A and B tumours having curative surgery with aneuploid tumours had a significantly higher recurrence rate (19/63, 30 per cent) compared with those with diploid tumours (6/70, 9 per cent) ($\chi^2 = 8{\cdot}8$, $P = 0{\cdot}005$)

Tumour cell DNA content is a predictor of higher risk of both local and distant recurrence after curative resection and may identify a group which would most benefit from adjuvant therapy

A new type of faecal occult blood test for detection of colorectal cancer

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Compliance is an important factor in screening for colorectal cancer by faecal occult blood test (FOBT) New types of FOBT improve compliance but their ability to detect cancer is not known. A new test, E-Z detect, has been compared with two established FOBTs.

A FOBT was performed by 976 patients with symptoms suggesting colorectal disease before a double contrast barium enema Patients were randomly allocated to one of three tests The ages of the patients were similar for all three groups and a total of forty-nine cancers were diagnosed The performance of the three FOBTs for the detection of cancer is shown in the *Table*.

	n	+ve	Sensitivity	Specificity	Predictive value
E-Z Detect	319	(13·2%)	57·1%	88·9%	19·0%
Haemoccult	315	(15·3%)	80·0%	88·3%	32·7%
Fecatest	342	(30·7%)	93·3%	72·2%	13·3%

E-Z Detect® is manufactured by NMS Pharmaceuticals, USA, Haemoccult® by Rohm Pharma, FRG and Fecatest® by Nordic Pharmaceuticals, USA

E-Z Detect has a low sensitivity for cancer, probably because stool does not come into direct contact with the test reagent, and may not be suitable for use in screening. Haemoccult has a high sensitivity and specificity confirming its suitability for cancer screening Fecatest has the highest sensitivity for cancer, equal to that for barium enema itself, and may be of use in symptomatic patients.

Intravenous epidermal growth factor (EGF) but not gastric EGF inhibits acid secretion

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Epidermal growth factor (EGF) applied topically, stimulates epithelial proliferation of the cornea and skin, but the pathway by which EGF inhibits gastric acid secretion (GAS) is not clear The presence of EGF in saliva and the beneficial healing of oral EGF on experimental gastric ulcers suggest that the luminal route is important. Parietal cells, however, are located deep in gastric glands and may not have direct access to EGF in the lumen.

We compared two routes of biosynthetic human EGF (IV and intragastric-IG) on canine GAS and correlated these results with EGF blood levels Stimulated GAS (Pentagastrin 0·3 μg/kg per h) was measured in five gastric fistula dogs in three phases (1) Saline placebo, (2) IV-EGF infused before study and (3) IG-EGF given in 200 cm³ saline 45 min before. Blood samples were drawn at 15 min intervals and stored for human EGF assay by RIA

EGF (dose/route)	GAS (meq H⁺/h)		
	1 h	2 h	3 h
Placebo	10·9±3·4	18·8±6·1	17·0±3·6
2 μg-IV	6·8±2·7*	14·1±5·2	14·6±6·4
10 μg-IV	0·5±0·5†	5·4±2·4†	10·2±3·4†
10 μg-IG	13·8±7·5	18·4±0·2	16·7±6·6
100 μg-IG	9·9±5·8	10·8±6·6*	10·7±5·4*

* < placebo GAS, $P < 0{\cdot}05$, † $P < 0{\cdot}01$

EGF in blood was detectable (5×10^{-8} M) only after IV-EGF (10 μg/kg) and only for the first 15 min The assay threshold is 10^{-9} M IV-EGF decreased GAS promptly while IG-EGF (100 μg) inhibited acid only in the second and third hour IV-EGF more effectively blocks GAS than IG-EGF Because the effect of IG-EGF was delayed by 1 h, it is possible that EGF was slowly absorbed into the blood (at subthreshold levels) and then suppressed GAS The data suggest that luminal EGF has little if any direct effect on parietal cells.

Is the 'acid antrum' clinically important after highly selective vagotomy (HSV) for duodenal ulcer (DU)?

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Parietal cells extend to the pylorus ('acid antrum') in 10 per cent of stomachs examined at post mortem[1]. Highly selective vagotomy (HSV) denervates the acid secreting gastric corpus but leaves the antrum innervated; hence if the 'acid antrum' exists in patients with duodenal ulcer (DU) it may be a cause of recurrent ulceration (RU) after HSV

HSV with Grassi test was performed in 29 patients with DU. By means of the gastrotomy performed for the Grassi test, biopsies were taken from the lesser and greater curvatures—2, 4, 6, and 8 cm from the pylorus. The biopsies were stained with haematoxylin and eosin and examined by an observer who was unaware of the site biopsied Parietal cell density was graded from 0 to 2: 0 no parietal cells, 2 'normal' corpus density, and, 1 scanty parietal cells. An 'acid antrum' was present if all biopsies contained parietal cells at corpus density.

Each patient had standard acid secretory tests performed 7 days after HSV when basal acid output (BAO) and peak acid output in response to insulin (PAOI), sham feeding (PAOSf) and pentagastrin (PAOPg) were measured.

An acid antrum was found histologically in three of twenty-nine patients, but in only one case was this detected as an area of low pH using the Grassi test. The median acid outputs after HSV in these 29 patients are shown in the *table*.

	BAO	PAOI	PAOSf	PAOPg	(meq/h)
No acid antrum	1·12	1·63	0·74	19·89	
Range	(0–5·92)	(0–10·16)	(0–21·32)	(2·37–41·28)	
Acid antrum	0·38	0·00	1·84	18·42	
Range	(0–2·23)	(0–0·6)	(0–3·14)	(17·70–23·19)	

After HSV the acid output of patients with an acid antrum did not differ from that of patients without acid antrum. No patient has developed a RU at a median follow-up of 1 year. Although the acid antrum occurs in 10 per cent of patients with DU, there is no evidence to suggest that it is of clinical significance.

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Duodenal ulcers that do not heal refractory ulcers or refractory patients

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After 3 months therapy with H_2 receptor antagonists (H_2RAs), 7 per cent of duodenal ulcers remain unhealed[1]. Why these 'refractory' ulcers (RFDU) do not heal is unclear. H_2RAs may not suppress nocturnal acid secretion in patients with RFDU[2].

We studied 36 consecutive patients referred for surgery for duodenal ulcer (13 RFDU, 23 non-RFDU) Ambulatory intragastric pH was monitored for 24 h on placebo and on ranitidine 300 mg nocte Median (quartile) pH is shown in *Table 1*

	24 h	Night (00.00–08.00 h)	Day (08.00–24 00 h)
RFDU on placebo	1·4 (1·3–1·4)	1·1 (1·0–1·3)	1·5 (1·4–1·7)
Non-RFDU on placebo	1·4 (1·3–1·7)	1·3 (1·0–1·6)	1·6 (1·4–1·8)
RFDU on ranitidine	1·9 (1·6–2·5)	5·3 (1·8–6·8)	1·8 (1·5–2·1)
Non-RFDU on ranitidine	2·3 (1·8–3·0)	6·7 (4·2–6·9)	1·7 (1·6–2·2)

The 24 h acidity of patients with RFDU did not differ from that of patients with non-RFDU. Median (quartile) percentage acid suppression by ranitidine is shown in *Table 2*.

Table 2

	24 h	Night	Day
Patients with RFDUs	41% (28–61)	87% (56–98)	32% (5–58)
Patients with non-RFDUs	61% (36–67)	95% (83–99)	25% (1–46)

Ranitidine suppressed acid as potently in patients with RFDU as in patients with non-RFDU; however it gave <50 per cent inhibition of nocturnal acid in 3 of 13 patients with RFDU but in none of 23 patients with non-RFDU ($P<0{\cdot}05$).

Thus, ranitidine gives adequate suppression of nocturnal acid in most patients with RFDU. We suggest that these patients are erratic tablet takers. In a few patients with RFDU, ranitidine affords inadequate inhibition of acid. Acid suppression sufficient to heal ulcers in these patients may be achieved with higher doses of ranitidine, other drugs or surgery.

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Pepsin—a prime suspect in intensive care unit gastritis

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The role of pepsin in stress gastritis has been underplayed in contrast to that of acid Despite aggressive antacid and H_2 receptor therapy, gastric mucosal lesions cause significant morbidity and mortality in the critically ill We hypothesized that substantial amounts of pepsin are released under conditions prevalent in shocked or septic patients. Pepsin release was studied in specifically 'stressed' isolated gastric mucosa ($n=8$). Guinea pig mucosa was evaluated in Ussing chambers under graded exposure to hypoxia and endotoxin, with measurement of acid, pepsin, potential difference (PD) and resistance (R) Mucosal integrity was evaluated by light microscopy. Critically ill intensive care unit (ICU) patients (8) were compared to a control group (8) Pepsin was measured by ^{125}I-labelled albumin assay.

Ussing chamber ($cm^2\ h^{-1}$)	Pepsin (units)	Acid (μeq)	PD (−mV)	Resistance ($\Omega\ cm^{-2}$)
Endotoxin expts (5% CO_2)				
0·0 units/ml endotoxin	0·17 ±0·04	0·89 ±0·06	35·5 ±1·6	112±13
0·01 units/ml endotoxin	0·57 ±0·21	0·74 ±0·07†	35·1 ±1·4	135±16†
0·1 units/ml endotoxin	1·04 ±0·55	0·60 ±0·09†	29·9 ±1·3†	190±26†
O_2 expt CO_2 0%				
100% O_2	0·19 ±0·07	0·65 ±0·06	24·5 ±2·7	64±7
Room air	0·33 ±0·08†	0·02 ±0·03†	3·1 ±2·8†	244±21†
100% N_2	0·57 ±0·10†	0·008 ±0·005†	0·5 ±0·5†	460±37†

† $P<0{\cdot}001$

Endotoxin caused significant increase of pepsin release and R Acid secretion was inhibited in a dose-dependent manner. Hypoxia and anoxia increased pepsin and R but decreased acid and PD. Endotoxin-treated and hypoxic tissues demonstrated marked oedema and focal cell damage. Peptic activity was 325±133 units/ml in controls but 4390±1213 units/ml in critically ill ICU patients ($P<0{\cdot}01$). The luminal content of the 'stressed ICU stomach' contains much pepsin Thus major concentrations of pepsin, a potent mucolytic barrier breaker, are present either by cell injury or secretion This may significantly contribute to the development of the acute gastric mucosal lesions identified under conditions of ICU stress and may explain the relative failure of acid inhibitory therapy

The development and resolution of duodenitis

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The study aimed to describe the light microscopic changes in developing and resolving duodenitis under experimental conditions

Ten beagle dogs were used. The first part of the duodenum was exteriorized on the gastroduodenal artery. Whole explants were examined 1 week, 1 month and 3 months after explantation (6 dogs) In four dogs the explants were reimplanted after 3 months maturation, into the duodenum, and were examined 1 week and 1 month later.

After explantation both normal and abnormal mucosa was present Changes were confined to jejunal type duodenal mucosa only. At 3 months there was a characteristic loss of goblet cells with replacement by cuboidal and mucus containing cells. Ulceration occurred The shape of villi varied Mitotic activity increased markedly in the crypts, and was not observed in Brunner's glands The earlier explants (1 week and 1 month) showed similar changes with more extensive superficial ulceration

After reimplantation many normal areas appeared within a week. New epithelium was derived from adjacent normal villi. Brunner's glands and the crypts of Lieberkuhn appeared to regenerate from the actively mitosing cells in the base of the crypts. No fully normal mucosa was seen without the regeneration of Brunner's glands

We concluded· (1) duodenitis does not occur uniformly even in flat explants, (2) duodenitis affects jejunal type duodenal mucosa and has a characteristic light microscopic appearance, (3) mitosing cells in the base of the crypts appear to be responsible for the regeneration of Brunner's glands and the crypts of Lieberkühn; and (4) Brunner's glands may be essential for the maintenance of mucosal integrity.

Omeprazole induced hypergastrinaemia: the role of duodenal mechanisms

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Previous studies have suggested that conditions which maintain a high intragastric pH (including omeprazole) produce a hypergastrinaemia owing to excessive secretion associated with raised intra-anal pH. The role of duodenal mechanisms has not been investigated. We have previously demonstrated that chronic acidification of canine duodenum led to a marked suppression of the hypergastrinaemia from the antrum transplanted into the colon (ACT)[1]. This study examined the effect of raising the duodenal pH with omeprazole on gastrin release in this model.

Four beagle dogs were used and ACT with a gastroduodenostomy was constructed as previously described[1] Two months postoperatively omeprazole 20 μmol/kg was administered daily for 14 days The results are shown in the *Table*

Dog	Pre-operative gastrin (pg/ml)*	ACT gastrin (pg/ml)*	ACT + omeprazole gastrin (pg/ml)*
1	41·9 ± 6·6	47·5 ± 6·7	126·9 ± 8·5
2	30·5 ± 4·5	36·5 ± 4·2	129·0 ± 14 2
3	32 2 ± 3 7	45·2 ± 5·0	185·9 ± 27 2
4	39·3 ± 6 9	46 1 ± 5 5	159·6 ± 37 6
	$P > 0{\cdot}05$**		$P < 0\ 001$**

* Results expressed as mean ± s e.m.

** Student *t* test paired data

The gastrin release from ACT is suppressed as previously demonstrated; this suppression is lost with omeprazole The hypergastrinaemia cannot be attributed to antral mechanisms in this model as the whole antrum is transplanted into the colon. Loss of pH dependent duodenal inhibition over gastrin release due to a raised pH may have played a role in the omeprazole induced hypergastrinaemia. Duodenal homoeostatic mechanisms may be very important in the regulation of antral gastrin release.

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Immune and endocrine effects of major abdominal operations.

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Major abdominal surgery results in poorly understood immuno suppression that may predispose to sepsis[1] This study examine potential mechanisms which may relate to an altered endocrine milieu Immune and endocrine parameters were measured pre-operatively an 1 day postoperatively in 30 cancer patients undergoing majo abdominal surgery. T cell response to concanavalin A (Con A) wa measured and dual-marker phenotypic analysis of T cell (CD3, CD4 CD8) and monocyte (M3, M3-Dr) subsets was determined by FAC microfluorimetry Plasma cortisol, growth hormone (GH), insulin (Ins and glucagon (Glu) were measured by radioimmunoassay Mea (± s e.m.) values were as follows (*$P < 0{\cdot}05$, paired *t* test) (see *table*)

Group	Con A (stim. index)	CD4/ CD8 ratio	M3-Dr (%)	Cortisol (μg/ml)	GH (ng/ml)	Ins (ng/ml)	Glu (pg/ml)
Pre-op	62 ± 8*	2 1 ± 0 2	54 ± 5*	26 ± 4*	3 ± 1*	2 ± 0·04	227 ± 50
Postop	37 ± 5	1 7 ± 0 1	41 ± 5	51 ± 5	8 ± 2	2 ± 0·05	235 ± 24

To determine whether cortisol or GH directly mediat immunosuppressive effects, mononuclear cells from five healthy donor were pre-incubated for 24 h with cortisol or GH at the concentration (pre- and postoperative plasma levels) obtained in the study N significant effect on T cell response to Con A or M3-Dr expression wa noted.

Major abdominal surgery significantly decreased T cell activatio and M3-Dr expression, and augmented cortisol and growth hormon levels. The *in vitro* data, however, argue against a role for cortisol alon as a mediator of postoperative immunosuppression. As only Dr-positiv monocytes can present foreign antigen to the host, reduce postoperative M3-Dr levels may represent a critical abnormality o host defences following major abdominal surgery.

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Inhibitory effect of 2-deoxy-D-glucose on liver tumour growth in rats

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Malignant tissues exhibit a high rate of glycolysis. Therefore inhibitio of glycolysis might reduce tumour growth Glucose analogue restraining glucose phosphorylation is a feasible approach for thi purpose However, the systemic use of IV glucose analogues is limited b their general toxicity. We therefore tested the local application of th glucose analogue 2-deoxy-D-glucose (2DG) in an isolated live perfusion model in the rat.

Inbred Wistar rats were used A chemically induced coloni adenocarcinoma was propagated under the renal capsule weekly tumour cell suspension was injected into the liver which created localized liver tumour growth after 5 days. One group of rats was treate with isolated liver perfusion for 30 min with oxygenated blood throug the portal vein and hepatic artery simultaneously. To the perfusate wa added 400 mg/kg 2 DG. Tumour volume was estimated before perfusio and at death 10 days after end of perfusion. A second group of animal underwent a similar operation with isolation of the liver but withou perfusion They received instead the same dose of 2DG IV divided i five doses during 30 min during 5 days. Tumour volume was assessed a above The third group was kept as untreated control.

All animals survived the treatments

Perfusion	2DG ($n = 11$)	IV 2DG ($n = 11$)	Control ($n = 11$)
Before	7 40 ± 2 9	10·9 ± 0 3	14·5 ± 2 7
After	913 5 ± 172	1011·6 ± 194	2604 3 ± 375*

Tumour volume mm^3 (mean ± s d.)

* $P < 0{\cdot}01$ compared with perfusion and IV 2DG

The tumour growth was thus significantly reduced by 2-deoxy-D-glucose in this experimental liver tumour model in rats. As local application of the intervention in the tumour metabolism avoids the risk for systemic side-effects, this approach should be explored further

Tumour burden, hepatic ornithine decarboxylase activity and polyamine metabolism after hepatectomy

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Ornithine decarboxylase (ODC) is essential for liver regeneration, and tumour burden depresses hepatic ODC activity. This study measured the effect of tumour burden on hepatic ODC and polyamine metabolism after hepatectomy.

Eighty mice were inoculated subcutaneously with MC-26 mouse colon cancer in the interscapular region and the tumours were allowed to grow; forty mice were tumour-free. Controls and mice with tumours of 0·3 per cent ('early') and 3 per cent ('late') of body weight underwent 60 per cent hepatectomy, and were killed 4, 8, 12 and 24 h after hepatectomy. Livers at resection and time of death were assayed for ODC activity and polyamine (putrescine, spermidine, spermine) concentrations. No tumour-bearing mice had liver metastases

	Control ($n=10$)	'Early' tumour ($n=10$)	'Late' tumour ($n=10$)
ODC (pmol CO_2/mg protein per h)			
Basal	64±10	75±9	33±3†
4 h	103±3*	82±4†	82±4*†
8 h	74±4	87±7	85±5*
12 h	72±5	85±6	63±7*
24 h	54±4	57±4	46±4
Putrescine (nmol/g)			
Basal	3±1	12±1†	12±3†
4 h	14±3*	20±2	27±5*
8 h	55±15*	37±3*	42±7*
12 h	15±4*	27±10	56±10*†
24 h	12±4*	67±12*†	153±33*†

Spermidine and spermine concentrations were unchanged (†=significantly ($P<0·05$) different to control at that time point; *=significantly ($P<0·05$) greater than basal in that group; ANOVA) Tumour burden elevates basal hepatic putrescine concentrations, and post-hepatectomy both ODC activity and putrescine metabolism behave abnormally up to 24 h after surgery. Depressed hepatic ODC activity may be due to elevated hepatic putrescine concentration

Prevention of oxygen free radical generation may protect against the development of irreversible haemorrhagic shock

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The pathophysiology of irreversible haemorrhagic shock (IRS) remains unsolved. This study was designed to assess the role of oxygen free radicals in IRS. Fifteen mongrel dogs were rendered hypovolaemic to a level where irreversibility ensued. The treatment group ($n=5$) received allopurinol (50 mg/kg per day) and vitamin E (100 units/kg per day) for 48 h before haemorrhage in an attempt to prevent free radical generation Oxygen radical scavengers, superoxide dismutase, dimethyl sulphoxide, catalase, and N-acetylcystine were administered at the point of irreversibility Control animals ($n=10$) were given equal volumes of normal saline. There was no difference between the two groups in haemodynamic parameters The volume of blood shed was greater in the treatment group (47·8±0·6 ml/kg) when compared with the control animals (38·1±0·6 ml/kg) (mean±s.e.m., $P<0·001$). Duration of hypotension was greater in the treated group (211±11 min) when compared with the control group (171±14·4 min) (mean±s.e.m., $P<0·05$). The length of survival in the treated group (210±44·4 min) was longer than that in the control group (36±5·7 min) (mean±s.e.m., $P<0·001$). These results suggest that prevention of free radical generation with allopurinol and vitamin E may delay the onset of irreversibility. However, in this model the scavenging enzymes failed to reverse IRS once established.

Wounded hindlimbs release substances with ACTH-like immunoreactivity

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Leucocytes *in vitro* produce substance(s) with ACTH-like immunoreactivity in response to various stimuli[1,2] *In vivo* release of substance(s) with ACTH-like immunoreactivity by leucocytes has been suggested[3], but has not been demonstrated. We investigated whether the leucocytic infiltrate present at the site of injury produced ACTH. Five days after bilateral λ-carrageenan hindlimb injury[4], wounded ($n=7$) and pair-fed control ($n=6$) animals underwent isolated bilateral hindlimb perfusions[4] ACTH-like immunoreactivity was measured in the perfusion medium using specific antisera directed against ACTH (1–24). The injured hindlimbs released substance(s) with ACTH-like immunoreactivity (14·0±5·0 pg/min/100 g body weight, mean±s.e.m), whereas those from control animals did not (−4·2±3·7 pg/min/100 g body weight); $P<0·05$ by Student's unpaired *t* test. The ACTH-like substance(s) in the perfusion medium from injured hindlimbs were extracted onto glass and fractionated on a G-50 gel filtration column. Substance(s) with ACTH-like immunoreactivity were present in at least two fractions of different molecular weight, one with a molecular weight range similar to native ACTH(1–39), the other of larger molecular weight These data demonstrate that wounded hindlimbs released substance(s) with ACTH-like immunoreactivity This is the first direct evidence to our knowledge for the release of substances with ACTH-like immunoreactivity from extrapituitary tissue *in situ*.

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Effect of interleukin-2 administration on wound healing in Adriamycin-treated rats

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Adriamycin® (doxorubicin), an effective chemotherapeutic drug, is also a potent inhibitor of wound healing, decreasing scar collagen content and thus decreasing wound breaking strength Recent work has demonstrated that certain polypeptide growth factors are capable of stimulating fibroblasts to secrete collagen, thus enhancing wound healing The purpose of this study was to determine if interleukin-2 (IL-2), a T cell growth factor, could reverse the wound healing deficit caused by Adriamycin (Farmitalia Carlo Erba) Twenty-six male Fischer rats were divided into four groups: group 1 received 1 ml intravenous (IV) 5 per cent dextrose in water (D5W) and a continuous infusion of D5W (0·12 ml/day) via an intraperitoneally placed osmotic pump; group 2, IV D5W and continuous intraperitoneal recombinant, human IL-2, 45 000 units/day (0·12 ml/day); group 3, IV Adriamycin, 6 mg/kg (1 ml) and intraperitoneal D5W, group 4, IV Adriamycin, 6 mg/kg and intraperitoneal IL-2. Each rat received a 5 cm dorsal, full-thickness skin incision, closed with skin clips, which were removed on postoperative day 7 On postoperative day 21, the rats were CO_2 asphyxiated Two scar specimens were taken from each animal and subjected to wound breaking strength (WBS) analysis. The remainder of each wound was blindly examined histologically (haematoxylin and eosin stain) Weights were recorded regularly and complete blood counts, including differential white blood cell counts, were obtained upon killing. Student's *t* test was used to compare groups.

	WBS (g)	Weight change (%)	WBC (×1000)	Hgb (g)/ Hct (%)	Inflammatory cells	Wound fibroblasts	Capillary ingrowth
1	2608 ±182	↑2·0	7·7 ±0·7	15·6/43·9 ±0·4/±1·2	++	+	++
2	2708 ±122	↓1·6	7·4 ±1·1	15·5/43·6 ±0·2/±0·6	+++	++	+++
3	1549* ±117	↑20·8*	7·5 ±0·7	12·9/36·9* ±0·6/±1·8	+	+	+
4	2126*† ±118	↓17·3*	9·5* ±0·6	13·9/39·1* ±0·3/±0·9	+	++	++

$^*P<0{\cdot}05$ *versus* appropriate control group, $^\dagger P<0{\cdot}05$ *versus* group 3

The results show that (1) Adriamycin impairs normal wound healing, (2) IL-2 administration significantly improves the wound healing impairment caused by Adriamycin, (3) IL-2 appears to increase infiltration of inflammatory cells, fibroblasts and capillaries into the wound which may account for the observed increase in WBS.

Monocyte HLA-DR expression is a marker of infection

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Peripheral blood monocyte HLA-DR expression (MO_2DR) was studied in 50 normal subjects, 20 severely infected patients (of whom 9 died) and 18 elective surgery patients. The mean MO_2DR value of normals (88·1±12·5) was significantly greater than the mean MO_2DR value of infected patients (36·6±23·9) ($P<0{\cdot}01$). Elective surgery patients had normal MO_2DR values pre-operatively (90·3±2·0) and decreased MO_2DR on postoperative day 1 (56·6±9·3) ($P<0{\cdot}01$). Of 18 elective surgery patients, 15 made uneventful recoveries and had normal MO_2DR values by day 3, the other patients developed severe wound infections and had persistently low MO_2DR values until postoperative day 14. *In vitro* incubation with lipopolysaccharide (LPS) increases monocyte HLA-DR expression. After *in vitro* LPS incubation, mean MO_2DR values of normal subjects were 96·8±4·1, elective surgery patients always had normal MO_2DR values. After LPS incubation, 11 surviving septic patients had mean MO_2DR values of 86·8±6·8 which was significantly greater than the MO_2DR values for patients who died from sepsis (24·5±5·0) ($P<0{\cdot}01$). These data suggest that MO_2DR is a useful marker of infection and probably a predictor. Inability to increase MO_2DR values after LPS incubation may predict mortality.

Endotoxaemia in obstructive jaundice: biliary obstruction is more important than lack of intraluminal bile salts

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Gut-derived endotoxaemia has been implicated in postoperative infective and renal complications in patients with obstructive jaundice. It is postulated that absence of gastrointestinal (GI) bile flow allows the translocation and absorption of toxins from the bowel lumen. Current therapy, such as oral bile salts or lactulose, is directed towards reduction of portal absorption of endotoxin, but results of clinical trials have been variable. We postulate that biliary obstruction is the most important factor in the development of endotoxaemia and that absence of bile salts in the GI tract is a secondary effect.

An experimental biliary fistula was developed in the rat to divert bile from the common bile duct to the urinary bladder (choledochovesical fistula, CVF), bypassing the gut. This allows study of the effect of absence of intraluminal bile salts, without biliary obstruction. Portal and systemic endotoxin concentrations were measured in controls and 2 weeks after sham operation, CVF and bile duct ligation (BDL), using a quantitative chromogenic Limulus assay.

Significant portal and systemic endotoxaemia occurred in BDL, but not in CVF, and confirms that biliary obstruction, rather than lack of intraluminal bile salts, is the most important contributing factor in the development of endotoxaemia. This may explain the variable results of therapy based on a reduction of portal endotoxin absorption and suggests that endotoxin absorption may occur at other sites.

	Portal endotoxin concentration (pg/ml)	Systemic endotoxin concentration (pg/ml)
Controls ($n=10$)	133±80	141±82
Sham ($n=10$)	117±58*	85±59*
CVF ($n=15$)	493±171*	272±115*
BDL ($n=15$)	1332±125†	928±114‡

Values are mean±s.e.m. Significance of difference from controls. *not significant, $^\dagger P=0{\cdot}0001$, $^\ddagger P=0{\cdot}0004$, CVF *versus* BDL (portal $P=0{\cdot}0023$, systemic $P=0{\cdot}0014$), total bilirubin was elevated in BDL (201±12 *versus* 5·3±1·1 µmol/l) (Mann–Whitney *U* test)

Application of multiple linear regression in the estimation of peripheral resistance: is the crural–arch communication an important factor?

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Long-term patency of femorodistal grafting is improved where the calf vessels are in continuity with the pedal arch. However arch assessment and crural vessel continuity have been dogged by poor arteriographic visualization and damped or absent Doppler signals.

We have studied 35 consecutive patients undergoing femorodistal reconstruction. Pulse generated runoff (PGR) was used to assess the patency of each crural vessel and its relative contribution to the pedal arch. Two points were given to a biphasic wave, one point for a monophasic wave and no points for no signal. An additional point was given to each vessel that communicated with the arch. The PGR score was then compared with the peripheral resistance (PR) measured at the time of surgery.

There was a good correlation between the total PGR score and the PR, $r=0{\cdot}47$, $P<0{\cdot}05$. Using multiple linear regression (MLR) three resistance values were derived for: (i) overall (R_0); (ii) one vessel runoff (R_1); and (iii) three vessel runoff (R_3) groups. (There were insufficient numbers in the two vessel group for analysis.)

(i) $R_0=1{\cdot}53-0{\cdot}05(\mathrm{PT})-0{\cdot}16(\mathrm{AT})-0{\cdot}06(\mathrm{Peroneal})-0{\cdot}34(\mathrm{Arch})$
(ii) $R_1=3{\cdot}09-1{\cdot}03(\mathrm{PT})-0{\cdot}66(\mathrm{AT})-0{\cdot}66(\mathrm{Peroneal})-0{\cdot}65(\mathrm{Arch})$
(iii) $R_3=1{\cdot}02+0{\cdot}02(\mathrm{PT})-0{\cdot}13(\mathrm{AT})+0{\cdot}2(\mathrm{Peroneal})-0{\cdot}14(\mathrm{Arch})$
(PT, posterior tibial, AT, anterior tibial)

There was a significant correlation between the predicted resistances R_0, R_1 and R_3 and the observed resistances, $r=0{\cdot}59$, $P<0{\cdot}001$, $r=0{\cdot}96$, $P<0{\cdot}001$, $r=0{\cdot}56$, $P<0{\cdot}007$, respectively. Both the AT and arch appear to be major determinants in PR.

PGR is a quick and easy method of assessing calf vessel patency and arch communication. Success of femorodistal bypass has been shown to correlate well with resistance measured at operation. Using PGR it is now possible to derive a resistance measurement which will predict the intra-operative findings.

Reproducibility and reliability of cyto-immunological monitoring (CIM) of heart-transplanted patients (HTP)

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The simple and atraumatic CIM with a sensitivity of 85 per cent and a specificity of 90 per cent was proved to be a valid method for diagnosis of acute rejection of heart grafts. Endomyocardial biopsies (EMB) have to be used only to control the success of the medication during acute rejection.

CIM allows a reduction in the frequency of EMB in the postoperative phase of HTP. The construction of a receiver-operating curve provided a preliminary definition of an optimal operational point at >7 per cent LB. The correlation with EMB indicates that this index coincides with the intramural inflammatory events of the graft. Concerning the prognostic value of CIM, a life table analysis supports the hypothesis that recipients undergoing a moderate/severe rejection as their first inflammatory event have the highest risk.

As the three different statistical analyses used lead to the same result, it can be concluded that CIM with its high sensitivity and specificity gives good information about the extent of inflammation in the graft, thus providing a chance for early treatment and control of acute rejection.

In order to prove the reliability of the CIM, 48 cytological preparations of mononuclear cells from peripheral blood of heart transplanted patients were differentiated by 10 heart-transplant centres and the individual results evaluated statistically

The two centres with highest numbers of transplantations using CIM showed the best correlation with the reference centre. The correlation coefficient was $r=0·95$, the predictive value 96 per cent, and the sensitivity was 100 per cent.

The five best centres resulted in a correlation of $r=0·87$, a predictive value of 82·1 per cent, a sensitivity of 61·8 per cent and a specificity of 98·8 per cent.

This proves that in the hands of well-trained centres the CIM is a reliable and reproducible method to diagnose acute rejection of heart grafts and to distinguish them from infections

Treatment of anismus in intractable constipation with botulinum A toxin

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Severely constipated patients with outlet obstruction or anismus attempt to force stool through an inappropriately contracting anal sphincter. To date treatment of this condition has been unsatisfactory. Botulinum A toxin is now an established first-line treatment for blepharospasm and other dystonias since it relieves muscle spasm. Patients with anismus may be improved if they are able to void against a non-spastic anal sphincter. In order to test this hypothesis we have injected botulinum A toxin into the striated anal sphincter of seven female patients (age 54, 27–72, median and range) with intractable constipation and anismus diagnosed electromyographically on defaecating proctography. The patients were studied prospectively by measurement of anal canal pressures, anorectal angles and symptom scores (visual linear analogue technique) before and 4 weeks after the injection of the toxin.

	Before	After botulinum A toxin	P*
Maximal squeexe anal canal pressure (cmH_2O)	60 (35–135)	28 (12–50)	<0·01
Anorectal angle (degrees)			
Squeeze	72 (62–101)	85 (58–122)	<0·03
Strain	100 (73–116)	120 (80–153)	<0·03

There were no long-standing complications. Incontinence occurred in one patient but resolved as function returned. Botulinum A toxin significantly ($P<0·03$, Wilcoxon matched pairs signed rank test) decreased the symptom scores for the amount of straining, the difficulty with bowel action, the degree of abdominal pain and abdominal bloating.

The significant improvement in patients' symptom scores correlated with the objective evidence of sphincter relaxation Botulinum A toxin appears to be a promising, safe method of treating patients with anismus.

Defective prostaglandin E (PGE) metabolism in duodenal ulcer

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Orally administered prostaglandins suppress gastric acid secretion and enhance gastric mucosal protection, but the role of endogenously synthesized mucosal prostaglandins in health and duodenal ulcer (DU) is controversial. In a previous study we showed that in normal subjects dietary linoleic acid stimulates PGE synthesis and suppresses gastric acid secretion. This study was designed to assess endogenous PGE formation and metabolism in DU by defining the response of DU patients to dietary linoleic acid.

Gastric PGE output was compared in nine control subjects and seven patients with well documented, healed DU. Basal output of immunoreactive PGE was 498±110 ng/h in controls and 138±41 ng/h in DU patients ($P<0·01$). In contrast gastric output of the principal PGE metabolite, 13–14 dihydro 15-keto PGE_2 (PGEM), was 192±19 ng/h in controls and 840±439 ng/h in DU ($P<0·01$). The mean ratio PGE:PGEM was 5.2 in controls, 1·5·4 in DU. Following dietary linoleic acid, 3 g daily for 14 days, PGE output increased to 1298±475 ng/h in controls but was virtually unchanged (96±21) in DU Similarly, PGEM output increased to 1335±708 ng/h in controls but did not increase in DU subjects. There was a small, but significant, fall in pentagastrin-stimulated gastric acid output in control subjects (35·2±3·5 to 30·1±2·8 mmol/h) but not in DU (29·3±2·3 to 28·6±2·8 mmol/h).

Duodenal ulcer disease is associated with inherent defects of PGE metabolism. PGE breakdown is increased and the normal, physiological, synthetic response to essential polyunsaturated fatty acids is absent.

Altered protease–antiprotease relationships in plasma during severe acute pancreatitis: a role for α_1-protease inhibitor?

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Immunoreactive trypsin is present in the plasma of normal individuals and patients with acute pancreatitis (AP). Concentrations are higher in AP, and clearance of trypsin α_2-macroglobulin (α_2-M) complexes is impaired[1], but the dynamics of complex formation have not been studied Plasma samples were collected 20 s after intravenous injection of 1 mg [^{14}C] trypsin (370 kBq/mg) in 19 patients with AP studied on the day of admission to hospital (12 mild and 7 severe attacks by clinical criteria). The molecular distribution of radioactive trypsin was determined by gel filtration through Sephadex G200, locating α_2-M, α_1-protease inhibitor (α_1-PI) and low molecular mass (<40000) binding fractions (LMMBF) using marker beads, and measurement of total and fractionated sample radioactivity by liquid scintillation.

	Distribution of ^{14}C-trypsin in plasma (median % of total)			
	Severe AP		Mild AP	Normal
α_2-M	57	*	86	98
α_1-PI	11	*	5	2
LMMBF	28		6	0

* $P<0·02$, two-sample rank test

In severe AP there was impaired binding of trypsin by α_2-M, and increased temporary binding by α_1-PI. The large rise in plasma concentration of α_1-PI during severe AP may provide important augmentation of plasma antiprotease capacity Antiprotease activity may be inadequate during the early stages of the attack, before the acute phase response has developed

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Taurolidine reduces endotoxin-related mortality in the jaundiced rat

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Gram-negative sepsis remains a major cause of morbidity and mortality due in part to the absence of an effective anti-endotoxin agent Taurolidine, a new antiseptic agent, is a derivative of formaldehyde and the amino acid, taurine. It has potent anti-endotoxin and antimicrobial effects *in vitro* We have investigated the *in vivo* anti-endotoxin effects of Taurolidine in a jaundiced rat model which has been shown to be highly sensitive to endotoxin. Thirty male rats (150–300 g) were subjected to common bile duct ligation and division. Animals were randomly divided into a control and a treatment group. Both groups received an endotoxin challenge (*E coli* lipopolysaccharide, 10 mg/kg) intravenously The treatment group received a simultaneous bolus of Taurolidine, 100 mg/kg. There was no significant difference in serum bilirubin levels between the two groups (217±14·1 *versus* 198±14·4 μmol/l, mean±s.e.m.).

The results reveal a difference in both mean survival time (620±110 *versus* 1300±90 min; mean±s.e.m., $P<0\cdot001$, Student's t test) and mortality rates at 24 h (12 *versus* 1, $P<0\cdot001$, χ^2 test) between the groups. This study demonstrates that Taurolidine is a potent anti-endotoxin agent These results have important implications for surgical practice and properly controlled clinical evaluation of this agent is urgently required.

New specific cholecystokinin (CCK) receptor antagonist ameliorates surgically induced pancreatitis

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There is no specific therapy for the management of acute post-surgical or traumatic pancreatitis Current theory suggests that CCK plays a permissive role in the development of acute pancreatitis. We postulate that CCK receptor blockade may ameliorate this response. The effect of the new highly potent CCK receptor antagonist L364718 was evaluated in the guinea pig before and after pancreatic trauma Animals received L364718 (25 nmol kg^{-1} h^{-1}) from osmotic mini-pumps 24 h before and 4 h after surgery Control animals received either DMSO alone (vehicle) or laparotomy without trauma (each group $n=10$). Pancreatic tissue was uniformly traumatized by a haemostatic clamp in three groups.

	Pancreas weight (mg 100 g^{-1})	Amylase (Somogyi units)			
		0	24	48	72
Trauma	368±42	1268 ±47	1690 ±69	2535 ±96	1817 ±86
L364718 (−24 h)	219±21	1696 ±96	1698 ±130	1852 ±155†	2180 ±238
L364718 (+4 h)	202±23	1246 ±62	1371 ±78*	1495 ±130†	1980 ±161
Control laparotomy	236±28	1348 ±158	1363 ±206†	1646 ±139†	1763 ±226

* $P<0\cdot05$, † $P<0\cdot001$

The pancreatitis of the L364718 treated groups was obviously less oedematous and haemorrhagic compared with the severe traumatic pancreatitis in the untreated group. Histology (blind) confirmed marked amelioration in the treated groups showing no saponification and fewer inflammatory cells Pancreatic weight was elevated in untreated animals compared with the other three groups ($P<0\cdot01$) Serum amylase increase was completely abolished in the L364718 treated groups ($P<0\cdot001$) Thus CCK receptor blockade by L364718 significantly reduced the inflammatory response, glandular oedema and release of amylase when administered before or after induction of pancreatitis. L364718 has a bioactivity of 6–8 h, is non-toxic and absorbed orally. Its potent receptor blockade effects when administered either before or after the onset of pancreatitis suggest an important potential therapeutic role in the management of patients with pancreatitis

Lipid peroxidation products in the pancreatic tissue of patients with acute pancreatitis

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Oxygen free radicals (OFR) induce lipid peroxidation within the cell membranes, thus leading to tissue damage It was shown experimentally that OFR are involved in the early development of acute pancreatitis This study examines the role of OFR-induced lipid peroxidation in patients with acute pancreatitis (AP). The lipid peroxidation products, conjugated dienes (CD) and malondialdehyde (MDA) were determined in pancreatic tissue samples from 12 patients undergoing surgery for AP. The same tissue measurements were performed in 7 organ donors without pancreatic disease (controls). All tissue samples were examined by light microscopy. The histological findings and the serum levels of α-amylase and lipase were compared with the tissue concentrations of CD and MDA. The levels of CD and MDA in all patients with AP were with 9·5±4 and 39·1±9 nmol/mg protein, significantly higher than the controls (CD=3·1±0·5, MDA=15·5±3·0) The MDA tissue concentrations were 53±10 nmol/mg protein higher in acute necrotizing than in recurrent acute pancreatitis The CD levels, although elevated, did not differ between the various forms of pancreatitis. α-Amylase and lipase levels, measured pre-operatively, did not correlate with either the degree of tissue damage or with the MDA and CD levels in the pancreas The increased levels of CD and MDA suggest that OFR are also involved in AP. MDA levels seem to correlate with the severity of the disease

Pancreatic blood flow at micro- and macroscale in experimental pancreatitis

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Measurements of the pancreatic micro- and macrocirculation were performed to evaluate the pancreatitis-induced changes, using a novel model of acute experimental pancreatitis (AEP) Hypotension-induced side-effects were avoided by adequate volume replacement.

Pigs were anaesthetized and ventilated mechanically After laparotomy, splenectomy and gastrectomy the animals were enterotomized. Mean arterial pressure, mean pulmonary artery pressure and pulmonary wedge pressure were monitored as well as the pancreatic blood flow (Q), which was measured by an electromagnetic flowprobe placed around the portal vein. Pancreatic microcirculatory parameters were measured using fluorescence videomicroscopy after intravenous administration of FITC–Dextran 150 and FITC-labelled autologous erythrocytes. The pigs were randomly assigned to group 1 (control, $n=9$) or group 2 (pancreatitis, $n=10$) Pancreatitis was induced by intraductal infusion of sodium taurocholate. Measurements were conducted at baseline, then every hour during a 6-h period For statistical analyses the Friedman and Wilcoxon U tests were employed

Macrohaemodynamics Systemic circulatory parameters remained constant in both groups Q, pancreatic vascular resistance (PVR), arterial–venous O_2 difference (avdO_2) and O_2 consumption (O_2c) did not change in the control animals. In the pancreatitis group avdO_2 and O_2c decreased significantly

Microhaemodynamics. At baseline 41 per cent of the capillaries were perfused in both groups. The control animals showed a slight increase to 47 per cent at 6 h. In group 2 as soon as 5 min after taurocholate we detected two different areas: (a) areas developing persisting stasis, (b) areas which were continuously perfused up to the end of the experiments. In these areas the portion of perfused capillaries increased significantly to 67 per cent. This was accompanied by an extravasation of FITC–Dextran indicating an increase of macromolecular permeability. Histology of group 2 revealed focal necrotic as well as intact tissue

Since hypovolaemic shock, which is often associated with pancreatitis, was avoided by volume replacement in this new model of AEP, the observed haemodynamic changes were unaltered by systemic haemodynamic variables and are therefore caused by pancreatitis solely

		Baseline		1 h		6 h	
		group 1	group 2	group 1	group 2	group 1	group 2
Q	(ml min^{-1})	62	49	62	52	49	50
PVR	(mmHg min ml^{-1})	1·2	1·5	1·1	1·3	1·4	1·6
avdO_2	(mmHg)	2·5	2·9	2·4	1·6*†	2·6	2·3*
O_2c	(ml min^{-1})	1·5	1·6	1·5	0·8*†	1·4	1·1*†

* $P<0\cdot05$ *versus* baseline, † $P<0\cdot05$ *versus* control

The findings of an unchanged Q and PVR besides the reduced O_2c and $avdO_2$ are explained by the changes within the pancreatic microcirculation. Focal stasis was observed beside areas showing typical signs of inflammation: increase of macromolecular permeability and capillary recruitment, e.g. oedema and hyperaemia. Histology of the AEP glands resembled the haemorrhagic necrotizing pancreatitis observed in patients.

Plasma fibronectin and acute-phase protein fluxes during acute pancreatitis

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Fibronectin (FN) opsonizes noxious bacterial and particulate material, enhancing their adhesion to phagocytes. Decreased plasma FN levels are associated with poor prognosis in septicaemia, burns and severe acute pancreatitis (AP)[1], as are increased concentrations of acute-phase proteins, e.g. C-reactive protein (CRP)[2] The aim of the study was to investigate the relationship between fluxes in plasma FN and acute-phase proteins, and the severity of AP Plasma FN, CRP, α-1-acid glycoprotein (AAG), pre-albumin (PA) and transferrin (TF) were measured using immunochemical and immunoturbidometric techniques, in EDTA-treated plasma samples obtained on days 1, 3, 5 and 7 of 20 attacks of AP. Twelve 'mild' attacks were uncomplicated, whilst eight 'severe' attacks were complicated by organ system failure ($n=6$) and/or pancreatic necrosis ($n=2$).

		FN mg/l	CRP mg/l	AAG mg/dl
Day 1.	Mild	225 (163–314)	6 (6–97)	58 (27–109)
		*	*	†
	Severe	152 (107–278)	96 (6–239)	72 (51–165)
Day 3	Mild	207 (153–261)	80 (27–174)	79 (56–106)
		*	*	†
	Severe	127 (75–171)	193 (109–319)	114 (68–158)
Day 5·	Mild	179 (113–276)	78 (20–157)	94 (72–137)
		*	*	†
	Severe	113 (54–181)	156 (108–241)	129 (89–182)
Day 7:	Mild	197 (140–291)	35 (6–170)	104 (69–147)
		*	†	†
	Severe	150 (43–219)	84 (23–163)	149 (89–195)

Median values and ranges; $^*P<0\cdot002$, $^\dagger P<0\cdot02$, two-sample rank test

In severe attacks, FN concentrations fell significantly more whilst CRP and AAG values rose significantly There were reciprocal trends in FN and CRP, and in individual patients values were significantly inversely correlated (Spearman test $t=-4\cdot67$, $P<0\cdot001$) Plasma PA and TF values were more stable and did not differ significantly between groups. Reduced synthesis, redistribution or catabolism may explain falling plasma FN levels in AP, although the association with the acute-phase protein response suggests some degree of common control.

1 Wilson C, Maharaj D, Gemmell C, Imrie CW Can fibronectin predict the outcome of acute pancreatitis? *Br J Surg* 1988; 75· (abstract)

2 Mayer AD, McMahon MJ, Bowen M, Cooper FH C reactive protein. an aid to the assessment and monitoring of acute pancreatitis *J Clin Path* 1984; 37· 207–11

Influence of prolonged total parenteral nutrition (TPN) on the pancreas: morphological and exocrine pancreatic secretion (EPS) changes

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The role of TPN in acute pancreatitis is to facilitate bowel and pancreatic rest. The question continues to be which solution achieves the minimum stimulation of pancreatic exocrine secretion preserving the normal pancreatic structure and function. The aim of this work is to correlate histological and EPS (stimulated with cerulein) changes in rats with prolonged TPN using three solutions. Group I ($n=18$), control; group II ($n=18$), glucose (66 mg/g) and amino acids; group III ($n=18$), glucose (38·8 mg/g) +LCT (11 mg/g) and amino acids; group IV ($n=18$), glucose (38·8 mg/g)+LCT and MCT (5·5 mg/g, each) and amino acids. These solutions provided 1·46 mg N_2/g body weight resulting in improved nitrogen balance. In each group EPS (amylase, chymotrypsin and total proteins) was studied 3, 7 and 14 days after TPN

Groups III and IV had a significant reduction in the EPS compared with group II (19 to 26 per cent). An interesting finding was the observation of acinar cell death by apoptosis after 3 days of TPN and a significant increase in groups III and IV compared with group II

The pancreas' structure is well preserved in animals with TPN using glucose solution EPS was significantly reduced in animals in which the source of calories was mainly with lipid emulsions, associated with apoptosis as an index of acinar cell deletion.

Serial computed tomography (CT) scanning in acute pancreatitis

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One hundred and two patients with acute pancreatitis had abdominal CT scans on admission (within 72 h), at 1 week and at 6 weeks. Twenty-eight attacks were clinically severe, seventy-four clinically mild Ninety-three (91 per cent) admission scans, eighty-five (83 per cent) 1-week scans and seventeen (17 per cent) 6-week scans were abnormal The aetiology of the pancreatitis could be determined from 28 (27 per cent) of the admission scans, the CT sign of fatty liver having a specificity of 100 per cent for alcoholic aetiology Fourteen pseudocysts were detected by CT scanning, seven of which were present on admission Only those five pseudocysts with an area index (max AP × max transverse diameter, cm^2) $>15\,cm^2$ were clinically apparent and required treatment

The pancreatic size indices (max AP measurement of head × max AP measurement of body, cm^2) of those patients with severe attacks were significantly greater than those with mild attacks on admission, at 1 week and at 6 weeks ($P<0\cdot004$).

In conclusion, the chance of making a retrospective diagnosis of acute pancreatitis by CT scanning at 1 week was 83 per cent Thirty-six per cent of pseudocysts detected by CT were clinically apparent and only those with an area index of $>15\,cm^2$ required treatment. Patients with severe attacks had significantly greater size indices on admission and this difference remained significant at 6 weeks.

Effect of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and hydrocortisone on experimental tumour growth and metastasis

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It is claimed that anticoagulants may reduce metastasis and prolong survival[1]. Reduced mortality in colon cancer patients given prophylactic UFH has been reported[2] Recently introduced LMWH—shown to be more effective in DVT prophylaxis—may be more effective in controlling tumour dissemination.

In this study 170 WHT mice were injected either subcutaneously (SC) or intravenously (IV) with 10^6 NC tumour cells. The mice were randomized to receive daily SC saline, UFH, LMWH or hydrocortisone. They were killed 3 weeks later and the weight of tumour in the SC group or the incidence of lung metastases in the IV group was recorded Survival and metastatic distribution were assessed in a further 120 mice given daily saline, UFH, LMWH or hydrocortisone after excision of the tumour at 3 weeks in order to mimic the surgical setting

UFH and LMWH reduced the weight of tumour following s.c. implant (saline, 807±225 mg, UFH, 594±168 mg, $P<0\cdot01$, LMWH, 532±146 mg, $P<0\cdot001$) and reduced lung metastases (saline, 100 per cent; UFH, 20 per cent, $P=0\cdot0004$, LMWH, 30 per cent, $P=0\cdot0015$). Although there was no difference in survival between the heparin groups, the incidence of lymphatic metastases in the LMWH group was significantly less (saline, 79 per cent, UFH, 100 per cent; LMWH, 29 per cent, $P=0\cdot0072$). Hydrocortisone had no effect alone nor did it improve the effect of UFH or LMWH.

LMWH had a similar effect to UFH in controlling tumour growth but was more effective in reducing lymphatic metastases. Clinical studies are now required to confirm these experimental findings.

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2. Kohanna FH, Sweeney J, Hussey S, Zacharski LR, Salzman EW. Effect of perioperative low dose heparin administration on the course of colon cancer *Surgery* 1983, **93**. 433–8

Effects of low-dose perioperative interferon on the postoperative suppression of host antitumour immune responses

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Several components of the immune system have antitumour activity including natural killer (NK) cells, lymphokine activated killer (LAK) cells and cytotoxic T lymphocytes. If the immunodepression frequently associated with surgery also impairs NK and LAK activity then the survival of metastatic cells liberated during surgical manipulation of the tumour will be favoured. *In vivo* immune responses are regulated by cytokines such as interferons, and recombinant cytokines are available for clinical use We have studied the effects of surgery on antitumour immunity and examined the influence which the peroperative administration of recombinant human interferon alpha (r-HuIFNα) might have on any changes observed. Thirty patients with gastrointestinal cancer were randomized pre-operatively into a control group ($n = 15$) who received no interferon, or to a treatment group ($n = 15$) receiving seven daily doses of 2 mU r-HuIFNα subcutaneously starting on the evening before surgery Measurements on NK and LAK cell cytotoxicities and endogenous interleukin-2 (IL-2) production were performed one day pre-operatively and repeated on postoperative days 1, 3, 5 and 10 Mean percentage (±s.e.) NK and LAK cytotoxicities follow.

	Pre-op		Day 1		Day 3		Day 5		Day 10	
	NK	LAK	NK	LAK	NK	LAK	NK	LAK	NK	LAK
Controls	38 ±6	25 ±4	15 ±4*	19 ±5	18 ±4*	17 ±4*	17 ±4*	10 ±3*	24 ±5*	14 ±4*
r-HuIFNα	41 ±5	28 ±4	33 ±4†	23 ±4	37 ±5†	17 ±3*	31 ±5†	15 ±3*	24 ±6*	9 ±2*

Values are mean percentages ±s e ; *postop *versus* pre-op, $P < 0·05$ (paired *t* test), †r-HuIFNα *versus* controls $P < 0·05$ (*t* test)

IL-2 production was also significantly impaired in both groups on postoperative days 1, 3 and 5 ($P < 0·02$ in all cases). The postoperative suppression of NK activity, but not the suppression of LAK or IL-2 production, can be prevented by r-HuIFNα. IL-2 is necessary for LAK activity and we suggest that a combination of IL-2 with r-HuIFNα is required to augment all endogenous antitumour lymphocytotoxicity.

CEA and CA 19-9 in gastric juice and serum: an aid in the diagnosis of gastric carcinoma?

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In this study we have measured the concentration of CEA and CA 19-9 in serum and gastric juice samples of normal and gastric cancer patients. We have shown that a direct linear relationship exists between gastric juice pH and the detected CEA concentration in a radioimmunoassay so all gastric juice samples were buffered to the optimal pH, which is neutral. Serum and gastric juice (GJ) levels of CEA and CA 19-9 were measured in 40 patients with gastric cancer, and the normal range for the assay was defined in 64 normal patients. The normal ranges for CEA (95 per cent confidence intervals) were 3·7–7·6 ng/ml in serum and 42·7–83·8 ng/ml in gastric juice. The normal values for CA 19-9 were 9–17·4 ng/ml in serum and 153·9–546·2 ng/ml in gastric juice. The following results are quoted as percentage sensitivity (percentage specificity) in the identification of gastric cancer; serum CEA alone, 27·5 (13·3), GJ CEA alone, 68·3 (32·5), serum CA 19-9 alone, 55·6 (29·4); GJ CA 19-9 alone, 53·6 (31·3), all four measurements, 90·5 (50)

Measurement of the serum and gastric juice carbohydrate antigens used in this study lacks sensitivity in isolation, but in combination identified 90 per cent of gastric carcinomas.

Exocrine secretion of epidermal growth factor by the rat prostate

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The rat prostate contains epidermal growth factor (EGF) which may physiologically interact with membrane EGF receptors found on prostatic cells via paracrine secretion or with membrane EGF receptors in the female genital tract via exocrine secretion. In order to determine whether EGF appears in the rat prostatic exocrine secretion, a model was developed for the *in vivo* isolated perfusion of the rat prostatic urethra and collection of the prostatic secretory product Timed effluent EGF was determined by radioimmunoassay.

Baseline EGF secretion by the rat prostate was 0·03 ± 0·004 ng/min. The table shows the influence of various neuropharmacological agents.

Agent class	Agent	n	Dose (mg/kg)	EGF (ng secreted/ 30 min)
α-adrenergic	phenylephrine	34	5	3·58 ± 0·37
		5	1	3·57 ± 0·41
		5	0·1	2·48 ± 0·37
		5	0·01	<0·6
α_1 blockade	phenylephrine + prazosin	5	5 5	1·03 ± 0·03
α_2 blockade	phenylephrine + yohimbine	8	5	3·13 ± 0·29
β-adrenergic	isoproterenol	6	0·04	1·33 ± 0·29
Cholinergic	pilocarpine	10	5	3·17 ± 0·55
		5	1	2·24 ± 0·74
		5	0·1	<0·6
Cholinergic blockade	pilocarpine + atropine	5	5 0·8	0·58 ± 0·3
VIPergic	VIP	5	0·1	<0·6

Values are mean ± s.e m. VIP, vasoinhibitory polypeptide

Neither β-adrenergic agonists nor VIP stimulated EGF secretion. EGF appeared in the rat prostatic exocrine secretion in a dose-dependent manner under α-adrenergic and cholinergic stimulation

In situ nick translation method reveals DNA strand break in cultured and mouse tumour cells induced by the alkylating agent carboquone

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We determined the relationship of DNA strand breaks to the toxicity of carboquone (CQ), a synthetic alkylating agent, in HeLa cells *in vitro* and mouse sarcoma 180 (S-180) cells *in vivo*, using *in situ* nick translation[1] The HeLa cells were exposed to CQ in Lab-Tek tissue culture chamber/slides and were fixed with ethanol/acetic acid Mice bearing ascites S-180 cells were treated with CQ via the tail vein and the tumour cells were smeared and fixed on slide glass. The break sites in the DNA were translated artificially in the presence of *E. coli* DNA polymerase I and ^{3}H-labelled dTTP, and were visualized autoradiographically The DNA strand breaks appeared as early as 5 min in the CQ-treated HeLa cells and increased in a dose and time-dependent manner, i.e. 10·1-fold at 3×10^{-6} M in 60 min This level related reciprocally to clonogenicity of the cell. The DNA strand breaks appeared in the S-180 cells in a dose and time-dependent manner, i.e. 6·5-fold after the mice had been exposed to CQ at 3·6 mg/kg for 2 h. The level of DNA breaks is crucial for CQ cytotoxicity and the nick translation method provides a rapid *in situ* assay for determining antitumour drug-induced DNA damage of tumour cells

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Influence of the anti-oxidants, vitamins C and E, on tumour formation in an animal model

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Dietary factors have been implicated in both the aetiology and prevention of colorectal cancer, with anti-oxidants possibly conferring protection We have studied the effect of two common anti-oxidants, vitamins C and E, on tumour formation and crypt cell production rate (CCPR) in an animal model.

One hundred and twenty Wistar rats were divided into three groups: one receiving standard diet, one additional vitamin E (600 international units/kg standard diet) and the last, additional vitamin C (1 per cent in the drinking water) for a total of 25 weeks Half of each group received the carcinogen 1,2-dimethylhydrazine (40 mg/kg) commencing on day 1 of the diet, continued for 5 weeks All animals were killed at 25 weeks, and tumour yield and CCPR measured

	Type of tumour			Percentage of animals with tumour	No. tumours/ animal	CCPR
	Benign	Intermediate	Malignant			
Standard diet	1	0	34	75	1·70	1·70
Standard diet + vitamin E	0	4	28	67	1·78	0·77*
Standard diet + vitamin C	1	12	14	88	1·40	1·55

*$P < 0·02$ unpaired *t* test

CCPR was significantly reduced in the vitamin E group and the number of animals with tumours was lower, suggesting vitamin E may confer some protection against carcinogenesis. Vitamin C showed no such advantageous effect.

Inhibition of growth of human pancreatic cancer *in vivo* by somatostatin and tamoxifen

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Recent reports suggest some beneficial response with tamoxifen (TXN) in patients with pancreatic cancer but no objective data exist. We have shown inhibition of pancreatic cancer growing in nude mice with the somatostatin analogue SMS 201-995. Our purpose was to study the response of human pancreatic cancer to both these agents *in vivo*. Twenty-four nude mice were xenografted in both scapular regions with SKI, a transplantable human pancreatic cancer and randomized into four equal groups: control, SMS 201-995 100 μg/kg three times daily intraperitoneally; TXN 10 mg/kg subcutaneously every 2 days; both agents in combination for 8 weeks until killing. Tumour areas were measured with calipers twice weekly and at killing, both normal pancreas and tumour were excised, weighed and assayed for DNA, RNA and protein content. Tumour oestrogen receptors were measured by Scatchard analysis. There were no differences in bodyweight or pancreas size during the study.

Tumour oestrogen receptors: 5·3 fmol/mg protein, KD 0·2 nM

	Control	SMS	TXN	SMS + TXN
Tumour area (mm^2)				
Week 2	35 ± 2	22 ± 4*	48 ± 6	42 ± 4
Week 4	91 ± 8	53 ± 9*	63 ± 5*	67 ± 8*
Week 6	247 ± 14	150 ± 32*	160 ± 13*	157 ± 11*
Week 8	388 ± 36	254 ± 47*	294 ± 36*	252 ± 21*
At killing				
Tumour weight (g)	2·48 ± 0·19	1·71 ± 0·36	2·17 ± 0·27	1·71 ± 0·17*
Tumour DNA content (mg)	3·60 ± 0·50	1·32 ± 0·28*	3·09 ± 0·67	0·95 ± 0·21*
Tumour RNA content (mg)	10·27 ± 0·40	4·28 ± 0·89*	7·13 ± 1·16*	3·50 ± 0·73*
Tumour protein content (mg)	225 ± 14	108 ± 25*	174 ± 28	94 ± 23*

* Significantly less than control by analysis of variance ($P < 0·05$)

This is the first prospective study to show a real, and significant, reduction in the growth of human pancreatic cancer *in vivo* with tamoxifen. The combination of tamoxifen with somatostatin therapy may be more beneficial than either agent alone.

Precancerous lesions in the pancreas after short-term pancreaticobiliary diversion

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Long-term pancreaticobiliary diversion (PBD) induces adenomatous nodules in rat pancreas[1]. The tumour yield in this model is satisfactory, but the latency period is long (> 15 months). Premalignant atypical acinar cell foci (AACF) have recently been described in carcinogen (azaserine)-treated rats, 4–6 months after treatment. To test whether PBD promotes AACF, male Wistar rats (weighing 250 g) received intestinal transection (controls, $n = 20$) or PBD ($n = 15$). Another group ($n = 19$) received intraperitoneal azaserine ($20\,\text{mg kg}^{-1}\,\text{week}^{-1}$) for 6 weeks, but no operation. At 6 months pancreatic wet weight and histology were assessed. The number and size of AACF in tissue sections were determined and mathematically transformed into three-dimensional data. PBD doubled pancreatic wet weight from 2·92 to 5·24 mg pancreas per g bodyweight ($P < 0·001$). Acidophilic foci (the putative premalignant AACF phenotype) were not seen in control rats Of 15 PBD rats, 8 had acidophilic foci; the number ranged from 1 to 4 per section. In rats given azaserine, acidophilic foci were rare. Compared with unoperated rats given azaserine, the number of acidophilic foci was doubled ($P < 0·05$) and the percentage volume of pancreas they occupied was five times greater ($P < 0·05$) after PBD Measurement of AACF provides a convenient short-term model for studying modification of pancreatic carcinogenesis. PBD enhances tumour development in this model.

1. Miazza BM, Widgren S, Chayvialle JA, Nicolet T, Loizeau E. Exocrine pancreatic nodules after long-term pancreaticobiliary diversion in rats. An effect of raised CCK plasma concentrations *Gut* 1987: **28** S1 269–73.

Effect of cyclosporin therapy in the rejection of ileal *versus* jejunal allografts

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Experimental evidence suggests that jejunal allografts are rejected as rapidly as ileal grafts despite their lesser content of lymphoid tissues. However it may be possible to postpone the rejection of jejunal grafts more readily by immunosuppressive therapy with cyclosporin. The rat model (BN→LEW rat strain) of orthotopic small bowel transplantation was used. In group I ($n = 6$) the proximal third of the jejunum with one-third of the mesenteric lymph nodes, in group II ($n = 6$) the distal ileal third with the entire mesenteric lymph nodes, and in group III ($n = 6$) the entire small bowel were interposed immediately distal to the ligament of Treitz after resection of an equivalent length of recipient bowel. These rats received cyclosporin 15 mg/kg body weight for 5 days intramuscularly, achieving a drug level of 600–1000 ng/ml (whole blood) Six rats (group IV) received entire small bowel grafts without cyclosporin therapy. After an initial weight loss during the first 5 postoperative days the rats in groups I–III gained weight until the 14–17th day when they developed diarrhoea This was followed by progressive weight loss and death after 26·3 ± 6·1 days (group I), 25·2 ± 6·1 days (group II) and 23·7 ± 4·2 days (group III) Inspection at autopsy showed graft encapsulation, stenotic segments and occasional enlargement of the mesenteric lymph nodes in groups I–III. Peritonitis was present in all animals Microscopically, loss of mucosa, submucosal fibrosis and bowel wall thickening was seen. The animals in group IV died of acute rejection (graft necrosis) after 10·8 ± 1·4 days.

These data show that short-term cyclosporin prolongs graft survival. Equal doses of cyclosporin, however, do not achieve prolonged survival of jejunal grafts in comparison with ileal or entire bowel transplants.

Influence of the lymphocyte content of small bowel allografts upon their rejection

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It has been suggested that the rejection of small bowel allografts could be mitigated by reducing their large content of lymphocytes as an immunological stimulus. This can be achieved by using jejunal rather than ileal segmental grafts or by irradiation of the graft/donor before transplantation. Using the rat model (BN→LEW rat strain) of orthotopic small bowel transplantation (SBT) without immunosuppressive therapy, five experimental groups were formed. In group I ($n=13$) the proximal jejunal third with a narrow mesenteric pedicle, in group II ($n=9$) the distal ileal third with the entire mesentery, and in group III ($n=6$) the entire small bowel were transplanted. In group IV ($n=7$) grafts were irradiated (1000 cGy) *ex vivo* immediately before SBT, and for group V ($n=6$) total body irradiation (1000 cGy) was given to the donors 4 days before SBT

Microscopic study of biopsies before SBT showed marked depletion of the lymphoid tissues in group V grafts but a normal appearance in group IV White blood cell counts in group V donors ($0{\cdot}28 \pm 0{\cdot}08 \times 10^3$) were markedly ($P<0{\cdot}05$) reduced in comparison with normal rats and the group IV rats ($8{\cdot}66 \pm 5{\cdot}48 \times 10^3$). All animals developed diarrhoea and progressive weight loss beginning on the 6–8th postoperative day, followed by death after 13·1±2·1 days (group I), 12·9±1·3 (group II), 9·5±1 (group III), 10·6±2·1 (group IV) and 9·5±1·8 days (group V) (no statistically significant difference, $P<0{\cdot}05$)

These results demonstrate that neither the reduction of lymphoid tissue in using jejunal segments or by transplanting grafts harvested from leucopenic donors postpone graft rejection in comparison to entire small bowel grafts. This indicates that the rapidity or severity of the rejection of small bowel allografts is not dependent to a major degree on the amount of lymphoid tissue transferred with the graft or on the length and type of the bowel segment used.

Adverse influence of recipient lymphoid resistance to *in vitro* immunosuppression on the outcome of kidney transplants

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Independent studies indicate that pretransplant lymphoid sensitivity to methylprednisolone (MeP) predicts the fate of kidney transplants in recipients receiving steroid/azathioprine (AZA) immunosuppression. This study was performed in 50 recipients of primary cadaveric transplants to determine whether mixed lymphocyte culture (MLC) responses to *in vitro* MeP, cyclosporin (CsA) and antithymocyte globulin (ATG) might indicate patients who are at increased risk from rejection despite receiving maintenance therapy with CsA, MeP and AZA and high-dose steroid and/or ATG antirejection therapy MLC responses of 29 recipients were sensitive to all three agents and 21 were resistant (4 to MeP, CsA and ATG; 5 to MeP and ATG, and 6 to MeP and CsA). The resistant group had a higher rate of graft loss from acute rejection (4/21 compared with 0/29, $\chi^2=6{\cdot}0$, d f =1, $P<0{\cdot}02$) and a higher incidence of biopsy-proven acute rejection episodes, with only 2 recipients not experiencing rejection compared with no rejection in 14 recipients from the sensitive group ($\chi^2=8{\cdot}7$, d.f.=3, $P<0{\cdot}05$). This study indicates that recipients at high risk of acute rejection can be identified by a pretransplant *in vitro* assay, a finding which could influence patient selection and the choice of immunosuppressive drugs

A new renal cooling device

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Warm ischaemia, experienced in renal transplantation, may cause significant renal dysfunction with irreversible histological change after 35 min[1]. A mean anastomosis time of 52±16 min (range 15–90 min) was recorded in 158 consecutive renal transplants at our institution Hypothermia protects against warm ischaemia but present application is limited by the inconvenience of available devices We have developed a compact cooling device independent of extraneous connections. It is a polyester laminate envelope containing a pulverized water-saturated polymer gel dispersed in silicone oil. Using a single kidney canine model cooling times of 60 and 90 min were assessed by serum urea, serum creatinine and urinary γ GT for 10 days Surface and core temperatures were monitored with microthermocouples. In the uncooled (control) group average surface and core temperatures were 36°C and 37°C compared with 7°C and 10°C in the cooled (test) group.

	Serum urea (mmol/l)	Serum creatinine (μmol/l)	Urine γ GT (units/l)
Normal canine values	4±1	113±17	55±30
Mean 60 min: control group	19±11	321±82	105±37
Mean 60 min: test group	9±3	142·5±19	57±31
Mean 90 min: control group	20±7	353±96	151±54
Mean 90 min· test group	9·5±5	156±22	80±41

These results are statistically significant at the $P<0{\cdot}05$ level and confirm the protective value of adequate hypothermia and demonstrate the ability of our device to provide it.

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Allo-antibody, primary non-function and cyclosporin A—an association with steroid-resistant rejection of renal allografts

J.D. Taylor, P.S. Veitch and P.R.F. Bell, *Leicester General Hospital, Leicester, UK*

Despite cyclosporin A (CyA), graft survival in the allosensitized patient is reduced by early graft loss from steroid-resistant rejection[1] Better HLA matching, more sensitive crossmatching from increased immunosuppression have all been advocated for the allosensitized patient In a consecutive series of 157 CyA-treated cadaver grafts transplanted for between 1 and 5 years there were 39 (25 per cent) patients with graft dysfunction due to rejection within 3 months of grafting One patient with a wound infection was not biopsied, and five received no antirejection therapy because of kidney rupture (four) and hyperacute rejection (one) First rejection episodes were treated with 0·5 g methylprednisolone on three successive days Treatment (R_x) failure ($n=17$) was graft failure within 3 months of the diagnosis of rejection. This was significantly related to the time from grafting of onset of rejection, allo-antibody as measured by panel reactivity (per cent PRA)[2], and simultaneous rejection with primary non-function (PNF–continuing need for dialysis after grafting) of the graft.

Table 1 Rejection <3 months

	Failed R_x ($n=17$)	Successful R_x ($n=22$)		Statistical test
Week of rejection—median	3	5	$P<0{\cdot}005$	(Mann–Whitney *U* test)
Peak %PRA—median	55%	0%	$P<0{\cdot}05$	(Mann–Whitney *U* test)
PNF with rejection	11	0	$P<0{\cdot}0001$	(Fisher exact test)

High-dose steroids were unsuccessful in treating rejection in grafts with PNF, and the association of PNF with failure of antirejection therapy probably reflects the severity of the rejection process The association of early rejection and allo-antibody with treatment failure suggests accelerated rejection in allosensitized patients.

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2. Opelz G, Terasaki PI. Recipient selection for renal transplantation. *Transplantation* 1976; **21**. 483–8

Renal allograft rejection: detection by ultrasound

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Acute rejection is the pre-eminent cause of a deterioration in graft function after renal transplantation. Clinical assessment of graft size is still held to be a useful indicator in this situation, but is clearly subjective. We have assessed ultrasound measurement of graft cross-sectional area in the diagnosis of rejection.

One hundred and forty-one episodes of deteriorating renal allograft function (creatinine rise $>30\mu$mol/l) were studied in ninety patients. Trucut biopsy under ultrasound control was performed in all cases and seventy cases of acute cellular rejection were identified In the absence of a proven urinary tract infection or obvious pelvicalceal dilatation, a greater than 10 per cent increase in renal cross-sectional area was defined as a positive scan indicative of acute rejection.

	Rejection	No rejection
Positive scan	64	13
Negative scan	6	58
Total	70	71

Using these criteria, scanning correctly diagnosed rejection in 64 out of 70 cases (sensitivity 91 per cent) and there were 13 false-positive scans (specificity 88 per cent). The investigation had a high predictive value when both positive (90 per cent) and negative (89 per cent). The error of the technique was found to be less than 5 per cent

This method is a simple, reproducible, non-invasive test for detecting rejection and deserves more widespread use.

Effects of acute limited normovolaemic haemodilution (ALNH) on intestinal healing

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Pre-operative ALNH (haematocrit >20 per cent) with retransfusion is utilized to reduce homologous transfusions. This study evaluated the effects of ALNH on trans-serosal oxygen tension (TsP_{a,O_2}), intestinal wall oedema, and intestinal healing Twelve male rabbits were randomized into two groups Group I = control, group II = ALNH induced by removal of 40 ml blood with simultaneous infusion of Lactated Ringer's in a 3:1 ratio to maintain blood pressure, followed by return of shed blood. A 6 cm segment of small bowel was resected and anastomosed end-to-end in all animals (8–10 sutures). Haematocrit (hct), colloid oncotic pressure (COP), and TsP_{a,O_2} were measured at three intervals: baseline, ALNH, and after retransfusion. Wet and dry weights and hydroxyproline were obtained at surgery and at killing on day 8. Tensile strength of anastomoses and normal bowel were measured on day 8

	Control ($n=6$)	ALNH ($n=6$)
TsP_{a,O_2} (baseline)	64 8	64·5
TsP_{a,O_2} (ALNH)		58 1
TsP_{a,O_2} (retransfusion)		73·1
Hct 1/COP 1 (%/mmHg)	39 3/17	41·5/18
Hct 2/COP 2 (%/mmHg)		29·0/12
Hct 3/COP 3 (%/mmHg)		36 0/16
Wet.dry ratio (at surgery/at killing)	4·7/4 4	3·2/4·2
Tensile strength (g)	452	457
Hydroxyproline (at surgery/at killing)	0·0432/0·0433	0·0603/0 0141

The data show that ALNH does not affect TsP_{a,O_2} ($P=$n s.), however it reduced COP ($P<0\ 001$) without increasing intestinal wall oedema ($P=$n s.) Tensile strength is not different ($P=$n s.), but the collagen content in the ALNH group is reduced by 24 per cent (although this is not a significant difference). We concluded that ALNH with retransfusion can be effectively used in clinical practice without impairment of intestinal healing.

Allosensitized canine renal allograft model of cyclosporin A-resistant rejection

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In clinical renal allotransplantation the allosensitized patient waits longer for a suitable crossmatch donor and is at an increased risk of graft loss from rejection with the histological features of vascular rejection.

Beagles were allosensitized against unrelated donors by blood transfusion, skin and kidney grafting. The lymphocytotoxic crossmatch test (CDC test) before renal allografting was positive The controls (group 1) were not allosensitized and received a primary renal allograft with cyclosporin A (CyA) 25 mg kg^{-1} day^{-1} orally for 21 days. Group 2 and group 3 were allosensitized with a positive CDC test before renal allografting with (group 2) and without (group 3) CyA Trough CyA levels were measured and the grafts biopsied percutaneously by Trucut needle twice weekly The results indicate the day that features of vascular rejection, namely glomerular thrombosis/necrosis, interstitial haemorrhage, and medial necrosis of arteries, were first seen Hyperacute rejection was not seen as all allografts produced urine for at least 24 h.

	Day of diagnosis of vascular rejection
Group 1	>21, >21, >21, >21, >21, >21
Group 2	2, 4, 6, 6, 6
Group 3	1, 2, 3, 3, 4, 5, 5, 5, 5, 5, 5

Group 1 *versus* group 2, $P<0\cdot05$, group 1 *versus* group 3, $P<0\cdot05$, group 2 *versus* group 3, $P=$n.s. (Mann–Whitney U test)

Allosensitized beagles had accelerated rejection of renal allografts with vascular features on biopsy In non-allosensitized beagles CyA prevented the appearance of these vascular features but was of no benefit in preventing allograft rejection with vascular features by allosensitized beagles with a positive CDC test. This canine model has the potential to be used for studying strategies for managing the allosensitized patient

Intestinal injury following total strangulation ischaemia and reperfusion

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Intestinal injury following partial ischaemia is significantly aggravated at reperfusion while reperfusion following total ischaemia does not seem to cause further injury[1]. To test whether detectable aggravation is prevented by the degree of injury in total ischaemia groups of rats ($n=10$ in each) were subjected to intestinal strangulation for 0, 1, 2, 5, 10, 20 etc., up to 90 min, followed by 60 min of reperfusion. Strangulation was achieved by means of a hydrostatic (pressure = 120 cmH$_2$O) cuff applied to the root of the mesentery. Biopsies for blinded microscopical examination were taken following ischaemia and reperfusion, respectively Tissue injury was graded from 0 (normal) to 8+; 5+ indicates villous, and 8+ transmural necrosis. Reperfusion was verified macroscopically in all experiments and by laser Doppler flowmetry in some. Ten minutes or less of ischaemia did not induce injury after ischaemia or at reperfusion. Prolonged ischaemia caused tissue injury proportional to the duration but reperfusion did not exacerbate the injury significantly.

	Ischaemic injury		Injury at 60 min of reperfusion	
Group	Median	Range	Median	Range
20	2+	0+ to 5+	1+	0+ to 4+
60	4+	1+ to 5+	5 5+	2+ to 6+
90	5+	2+ to 7+	6+	3+ to 8+

After intestinal strangulation, induction of total ischaemia reperfusion was not associated with significant aggravation of injury, regardless of the severity of the ischaemic injury itself

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Effect of cyclosporin on small intestinal vasculature

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There is evidence that cyclosporin A (CyA) nephrotoxicity is caused by vascular changes mediated through the prostaglandin system The mucosal blood supply is a prime target in small intestinal transplant rejection and this study was undertaken to establish whether CyA can cause microvascular impairment independent of immune-mediated damage A projection X-ray microscope, resolving structures of 1 μm diameter, has been used to study small intestinal microvasculature including the submucosal capillary plexus.

Three groups of six (Lewis × Brown Norway) F$_1$ rats were examined. (a) CyA in therapeutic doses (15 mg kg^{-1} day^{-1} orally for 7 days), (b) CyA in toxic doses (50 mg kg^{-1} day^{-1} orally for 28 days), and (c) normal controls.

Animals were perfused with a 20 per cent w/v barium sulphate suspension at 37°C and 85 mmHg. Specimens of small intestine were prepared and fixed in buffered formalin Radiographs were examined using the Kontron IPS image processing and analysis system to measure intestinal vascularity

	Control	CyA (15 mg kg^{-1})	CyA (50 mg kg^{-1})
Percentage area of field occupied by vasculature	8·8 (7·4–10·2)	4·5 (3·2–6·8)*	6·6 (5·2–8·2)*

Median and range values are given.
* $P<0·05$, Mann–Whitney *U* test

In cyclosporin-treated rats, in addition to impairment of the capillary plexus, the mural traversing arteries (diameter, 25–35 μm) were attenuated. Larger mesenteric vessels remained relatively unaffected These results suggest that, apart from its established nephrotoxic potential, CyA (even in therapeutic doses) may have an additional deleterious effect on small intestinal microvasculature

Gut peptide responses to superior mesenteric artery occlusion

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The intestine contains several vaso-active peptides: the vasodilators include vaso-active intestinal polypeptide (VIP), α- and β-calcitonin gene-related peptide (a- and b-CGRP) and substance P (SP), and the vasoconstrictors somatostatin (Som), peptide YY (PYY) and neuropeptide Y (NPY) Since the mechanisms of the intestinal vasodilatory response to ischaemia are unclear we investigated the possible role of these peptides The superior mesenteric artery (SMA) was occluded in 24 Wistar rats (groups A, B, D, E, $n=6$ in each) for 5 (A, B) or 20 (D, E) min followed by 3 min of reperfusion (B, E) Arterial blood samples were obtained at the end of each experimental period. Controls (C, $n=6$) were subjected to the same procedure without SMA occlusion Plasma peptide concentrations were measured by specific radioimmunoassays

A significant rise in plasma VIP was observed in groups B and E and in b-CGRP in group E. The other peptides did not change.

Group	VIP	b-CGRP	aCGRP	SP	Som	PYY	NPY
A	7±2	35±7	21±4	13±3	24±5	34±9	85±15
B	37±4*	34±6	29±5	19±2	37±12	47±7	150±43
C	11±4	23±1	23±3	15±2	25±7	31±3	90±22
D	5±2	26±3	25±4	17±3	16±2	26±7	90±25
E	31±3†	49±3*	36±3	21±3	25±4	35±5	119±26

Values are mean±s.e.m. (fmol/ml), *$P<0·001$, †$P<0·002$ *versus* control (ANOVA)

These findings demonstrate release of only those vasodilators of intrinsic nervous system origin, VIP and b-CGRP, from the ischaemic intestine The release of VIP occurs early, while that of the more potent b-CGRP occurs during prolonged ischaemia The specificity of these responses provides interesting new information on the mechanisms of intestinal ischaemic vasodilation.

Mucosal autografts in experimentally induced short bowel syndrome (SBS)

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SBS is the result of an inadequate area of functional small intestine Previous studies have shown that *in vitro* tissue uptake of 3-O methyl glucose is a suitable method to assess jejunal and colonic glucose transport[1]. We have used this technique to study the function of jejunal mucosa 5 days after transplantation to denuded colon in rats

Experiment 1	1 cm^2 denudation of jejunal or colonic mucosa ($n=8$).
Experiment 2.	1 cm^2 jejunal graft to colon ($n=10$)
Experiment 3	1 cm^2 jejunal graft to colon and 80 per cent small bowel resection ($n=15$).
Experiment 4	1 cm^2 jejunal graft to colon and gastrocolic anastomosis ($n=7$).

The results are expressed as a mean±s.e and are compared to a control group of eight rats. The results are given in the table. Statistics are by Student's *t* test

Experiment	3-O methyl glucose uptake (μmol 5 min^{-1} mg tissue^{-1})	Significance
Control	Colon: 0·12±0·03	—
	Jejunum: 0·68±0·08	—
Experiment 1	Colon: 0·09±0·02	n.s
	Jejunum 0·53±0·07	—
Experiment 2	Colonic jejunal graft: 0·14±0·03	n s.
Experiment 3	Colonic jejunal graft: 0·58±0·07	$P<0·01$
Experiment 4	Colonic jejunal graft: 0·13±0·03	n.s

Macroscopic examination of the denuded colon showed re-epithelization In those animals in which small bowel was not resected functional metaplasia of the graft occurred. After 80 per cent small bowel resection and transplant, jejunal grafts maintained their small bowel absorptive function It is unlikely that this is the result of bulk nutrient presentation because after gastrocolic fistulae the jejunal grafts lose their normal absorptive capacity Long-term experiments to determine the efficacy of this novel approach to SBS are indicated

1 Banerjee AK, Raja K, Peters TJ. The effect of insulin on jejunal glucose absorption. *Clin Sci* 1988; **74** (suppl 18). 69P.

Morphological changes of the enteric nervous system (ENS) in Crohn's disease

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The segmental character of the lesion and altered intestinal motility in Crohn's disease (CD) point to a possible implication of the ENS Up to now only separate elements of the ENS have been investigated by conventional staining methods. The aim of the present study was to analyse structural changes of the entire neural functional unit and to correlate these findings with the density of the inflammatory infiltrate within the lesion

The formalin-fixed, resected gut specimens of 11 patients with CD were studied at predefined multiple sites along each specimen The ENS was marked with an indirect peroxidase method using a polyclonal antiserum against the neural S-100 protein as primary antibody This immunoreactivity allows a selective staining of all neural structures with the exception of ganglion cells. The data were analysed considering the inflammatory and postinflammatory changes and the topography of the CD lesion Compared with normal controls we found: (1) in the lamina propria mucosae: an increased number of nerve fibres; (2) in the lamina submucosa: an increased number and splitting phenomenon as well as a proliferation of nerve fibres; (3) in the lamina muscularis propria: similar changes of the neurones as compared with the lamina submucosa. These changes were primarily found within the CD lesions but in some cases also, although to a lesser extent, in the histologically normal margins of the resected specimens.

The observed histomorphological changes of the ENS in CD can be understood as degenerative and, secondarily, regenerative. They appear in segments under the light microscope as free of CD lesions and thus might be regarded as early changes. We explain these findings with a possible initial (toxicogenic?) damage to the axons and reactive proliferation of surviving axons, as this is known to occur in peripheral nerves after amputation.

α_2-Adrenergic agonists mediate intestinal absorption in the isolated perfused ileum

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Norepinephrine (NE) is a sympathetic neurotransmitter, released from autonomic nerve terminals within enteric neural plexuses and intestinal mucosa, which alters intestinal vascular resistance and intestinal transport. This study was designed to study the effect of selective α-adrenergic agents on intestinal perfusion pressure and transport. Rabbit ileal segments (20 cm) were vascularly perfused ($n=28$) at 1·5 ml/min using a sanguineous buffer solution. The intestinal lumen was perfused with an isotonic solution containing ^{14}C-PEG as a non-absorbable marker. Net fluxes (F) of H_2O (μl/min) and electrolytes (μEq/min) were calculated, and perfusion pressure (PP; cmH_2O) was measured during 20 min basal, experimental, and recovery periods. Data are expressed as the change in flux (ΔF) and the change in perfusion pressure (ΔPP) between basal and experimental periods.

Agent	(receptor, n, dose)	ΔPP	ΔF H_2O	ΔF Na^+	ΔF Cl^-
NE	($\alpha_1+\alpha_2$, 7, 0·4 μg/min)	27±5*	+20 ±8*	+2·6 ±1·4	+2·1 ±0·8*
PHE	(α_1, 6, 7·6 μg/min)	83±8*	−4 ±6	+0·1 ±0·9	−0·4 ±1·0
CLON	(α_2; 8, 10 μg/min)	2±1	+20 ±8*	+3·1 ±1·3*	+3·0 ±0·9*
NE+ YOH	(α_2 antag, 7; 1 μg/min)	25±4*	+1 ±5	+0·1 ±0·7	−0·3 ±0·5

NE, norepinephrine, PHE, phenylephrine, CLON, clonidine, YOH, yohimbine, *$P<0{\cdot}05$ by Student's t test, +ΔF, absorption

NE increases perfusion pressure and causes absorption. PHE, a selective α_1 agonist, increases perfusion pressure, but does not affect transport. CLON, a selective α_2 agonist, stimulates absorption without effect on perfusion pressure. YOH, a selective α_2 antagonist, has no effect on NE-induced increases in perfusion pressure, and prevents NE-induced absorption. α_1-Adrenergic agonists modulate intestinal vascular resistance, while α_2-adrenergic stimulation causes intestinal absorption. Endogenous NE, released from autonomic neurons, may be a physiological regulator of intestinal vascular resistance and transport, acting via separate α-adrenergic receptor systems.

Clustered gastrointestinal (GI) hyperactivity in partial intestinal obstruction: detection by surface vibration analysis (SVA)

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GI contraction 'clusters' with alternating quiescence are detected by intraluminal manometry, in partial intestinal obstruction[1]. This invasive method is unsuitable for ill patients. Surface vibration analysis (SVA) is a non-invasive measurement of GI energy and activity patterns.

In this study SVA recordings, taken for 3 h after a test meal in 9 patients with suspected subacute intestinal obstruction, were evaluated against those of 36 healthy volunteers. Obstruction was proved in 7 patients (5 laparotomy; 2 X-ray) and disproved in 2 (laparotomy).

SVA showed regular peaks of GI hyperactivity lasting 3·53±0·1 min (mean±s.e.m.) alternating with quiescence lasting 4·6±0·3 min, in all patients with proven obstruction. This alternating pattern occupied the total recording interval (210 min) in 3 patients and was partial in 4.

Volunteers and non-obstructed patients had a more sustained postprandial response. Activity peaks were of low amplitude, irregular and fewer in number (6·2±0·7) when compared with obstructed patients (13·1±1·8) ($P<0{\cdot}01$; Mann–Whitney U test). Total SVA energy values were greater in obstructed patients (405·728±52·837) than in normals (195·433±19·040) or non-obstructed patients (121·148±55·728) ($P<0{\cdot}01$, Mann–Whitney U test).

SVA defines a GI pattern of alternating hyperactivity and quiescence in partial intestinal obstruction.

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Therapeutic effect and mechanism of immunochemolymphocytotherapy against a murine malignant ascites

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We previously reported that pre-administration of a streptococcal preparation, OK432, followed by low-dose cyclophosphamide (CY) augmented the effect of adoptive immunotherapy (AIT) using IL–2-cultured lymphocytes. In this study, we examined the effective mechanisms of the sequential immunochemolymphocytotherapy.

BALB/c mice were inoculated with MOPC104E-plasmacytoma intraperitoneally and then treated with 1KE of OK432 on days 8 and 9 post-inoculation and CY (1 mg/kg) on day 10. On day 11, intraperitoneal (IP) cells of tumour-bearing mice (treated with OK432 or OK432 plus CY) were collected and mixed with cultured lymphocytes (CL) and/or autologous spleen cells and then transferred to normal mice to test the transplantability. CL were propagated from tumour-bearer-spleen cells stimulated with conconavalin A, IL–2 and tumour antigen for 11 days.

The transfer test revealed that OK432 augmented the sensitivity of IP cells to CL, and that CY augmented the antitumour effect of the host's spleen cells. Analysis using anti-thyl suggested that T cells in IP cells and in spleen cells are responsible for such effects. Therefore, AIT after the immunochemotherapy was found to show a therapeutic effect via a host-mediated mechanism.

Role of prostaglandins in the vascular response to photodynamic therapy

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Photodynamic therapy (PDT) of malignant tumours may involve the interruption of tumour and peritumour microcirculation. We studied the effect of light activation of the photosensitizing drug dihaematoporphyrin ether (DHE) on rat subcutaneous arterioles and the modulation of these effects by cyclo-oxygenase inhibitors, indomethacin and acetyl salicylic acid (ASA).

Male Sprague–Dawley rats were anaesthetized with pentobarbital (50 mg/kg, intraperitoneally) 48 h after DHE administration (10 mg/kg, intraperitoneally). A dorsal skin flap was raised and subcutaneous arterioles (150–200 μm) were exposed to light (630 nm, 60 J/cm^2) from a laser Doppler velocimeter which was used to activate DHE and record changes in blood flow. In addition to DHE, animals received either indomethacin (1 mg/kg, intraperitoneally, $n=15$), ASA (100 mg/kg, intraperitoneally, $n=10$) or saline ($n=7$) 3 h before light activation. Light activation for 5 min, 48 h after DHE administration, resulted in a significant reduction in blood flow to 58 per cent (±7 per cent s.e.m.) of initial blood flow ($P<0{\cdot}05$). This effect was significantly inhibited ($P<0{\cdot}05$) by ASA (98±8 per cent s.e.m.) and indomethacin (87±8 per cent s.e.m.). These data show that PDT causes significant reduction in blood flow in normal arterioles and that this effect was clearly inhibited by ASA and indomethacin indicating that prostaglandins or thromboxane A_2 are important in microvascular response to PDT.

Improved tumour targeting of biodegradable microspheres with angiotensin II

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Hepatic arterial chemotherapy for liver metastases increases tumour exposure to cytotoxic agents. Further developments in regional therapy have been the use of microspheres incorporating chemotherapeutic drugs or ionizing radiation[1,2] which embolize in the tumour-bearing liver when arterially injected

It is known that tumour blood vessels cannot vasoconstrict[3] in response to angiotensin II (AII) This study assesses the value of AII in increasing uptake of radiolabelled albumin microspheres (^{99m}TcMSA) by tumour relative to normal liver. Six patients with colorectal hepatic metastases and indwelling hepatic arterial catheters each underwent three scintiscans. Computerized tomography was performed to allow three-dimensional image analysis A tin colloid scan delineated tumour regions. Hepatic arterial perfusion with ^{99m}TcMSA was performed alone, then after an infusion of AII.

Differences in microsphere uptake attributable to AII were assessed in 15 tumour regions in 6 patients. The median ratio of radioactivity between tumour and normal liver was 2·5 (range 0·85–17), which improved to 7 (range 2·9–11) after AII The mean improvement in ratio (2·5 ± 1·3 s.d.) was statistically significant ($P<0·05$, paired *t* test)

We conclude that AII produces a significant increase in microsphere uptake by liver metastases, and may prove valuable in treatment.

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Increased arteriovenous shunting and extrahepatic diversion associated with the use of hepatic arterial microspheres for liver metastases

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Arterial therapy for liver metastases may be enhanced by temporary blood flow stasis using 45 μm degradable starch microspheres However, intrahepatic arteriovenous (A-V) shunting and extrahepatic abdominal perfusion (EHP) were observed on arterial macroaggregated albumin (MAA) scans in seven patients receiving such regional therapy, and this could reduce the advantages.

We have studied the effect of tumour and 50 μm microspheres on both A-V shunting and extrahepatic diversion of hepatic arterial flow in four groups of rats. (A) controls ($n=17$), (B) a group with liver metastases established by intraportal injection of 10^6 MC28 sarcoma cells ($n=18$); (C) a group with liver metastases given hepatic arterial 50 μm microspheres ($n=12$), and (D) a group receiving intra-arterial 50 μm microspheres only ($n=13$)

Shunting to the lungs and EHP to the stomach and spleen were measured by hepatic arterial injection of ^{113}Sn-15 μm microspheres Organs were excised for radioactivity counting. The percentage hepatic replacement with tumour (PHR) was also measured

	Group A	Group B	Group C	Group D
Animals with >1% shunting to lungs	1/12	5/18	10/17	6/13
A-V shunting	8%	28%	59%*	46%
EHP%				
median	1·1	1·6	36	16
(range)	(0–23)	(0–44)	(8–49)†	(3–44)‡

*$P<0·02$ *versus* GpA, †$P<0·0001$ *versus* GpA/B, ‡$P<0·001$ *versus* GpA, $P<0·005$ *versus* GpB

Shunting to the lungs (>1 per cent) occurred in significantly more animals in group C (59 per cent) compared with controls (8 per cent) EHP was significantly associated with 50 μm microspheres irrespective of the presence of tumour

Blockading 50 μm microspheres can increase shunting and extrahepatic diversion of hepatic arterial flow. This emphasizes the need for careful monitoring when using microspheres clinically.

Improved detection of colorectal liver metastases by intra-operative ultrasound

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The identification of occult hepatic metastases is essential to stage patients with colorectal cancer accurately. We have performed intra-operative ultrasound at laparotomy using a sterilizable probe on forty patients with colorectal cancer, who also all underwent liver palpation pre-operative abdominal ultrasound, and CT scanning of the liver the results of which were unavailable to the intra-operative ultrasonographer. In all cases both lobes of the liver were scanned by intra-operative ultrasound from the anterior and posterior surfaces The mean duration of the examination was 11·0 min Fourteen of forty patients had metastases detected.

The number of patients with metastases detected by each technique was palpation, 9; pre-operative abdominal ultrasound, 3; intra-operative ultrasound, 12; and CT scan 7.

Of the 14 patients with metastases detected, metastases were missed by intra-operative ultrasound in 2 patients (small, easily palpable surface metastases) and by CT scan in 7 patients. Intra-operative ultrasound detected deeply situated metastases down to a diameter of 7 mm.

In four patients whose livers were normal to palpation, pre-operative abdominal ultrasound and CT scan, liver metastases were detected by intra-operative ultrasound. Intra-operative ultrasound appears to be the most accurate technique available for the detection of liver metastases.

Cancer: a metabolic parasite

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We have tested the hypothesis that malignant tissue is a metabolic parasite in the sense that it has a higher rate of protein synthesis than the tissue in which it arises, and that as a result substrate that would normally be incorporated into host protein synthesis preferentially goes to protein synthesis in the cancer

We have used the primed constant infusion of ^{14}C-leucine administered before and during cancer surgery in seven patients with cancer cachexia (malignant disease with weight loss greater than 15 per cent of well bodyweight). By taking samples of muscle, liver, skin and the cancer, we have determined fractional rate of protein synthesis (FSR) in these tissues.

Tissue	Fractional synthesis rate
Muscle	2·3 ± 0·3% per day
Skin	2·7 ± 0·3% per day
Liver	18·5 ± 3·0% per day
Cancer	18·0 ± 4·0% per day*
Tissue of cancer origin	6·0 ± 1·5% per day

*Significantly different from corresponding value in tissue of origin $P<0·05$

From these data, FSR of protein is higher in malignant tissue than in the tissue in which the cancer arises In addition, the FSR of the cancer is exceeded only by that of the liver, and the FSR of malignant tissue is three times greater than the FSR of the tissue the cancer arises in These data have implications regarding the use of parenteral feeding to replete cancer patients, and we are currently addressing this issue.

Predictive value of nucleolar organizer regions in prostatic carcinoma

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Prostatic carcinoma varies from a biologically indolent to aggressive tumour, without a reliable predictor of disease outcome Nucleolar organizer regions (NORs) are loops of DNA which transcribe RNA and mirror cellular proliferative capacity and degree of differentiation. The predictive value of NORs in tumour tissue is unknown. We have tested the hypothesis that NORs have prognostic significance in prostatic carcinoma.

Sections from 45 patients with prostatic carcinoma and 10 with benign hypertrophy were coded and stained for NORs. Three groups of malignant patients were studied. Group 1 ($n=20$) had metastases at presentation. Group 2 ($n=17$) had no metastases at presentation and remained free of metastases 4 years later at review. Group 3 ($n=8$) were initially free of metastases but later developed metastases (mean interval 1 year). The mean number of NORs per nucleus was determined using oil-immersion microscopy without knowledge of patient groupings.

NOR score	Benign	No metastases	With metastases	Developed metastases
Median	2·8†	4·78†	5·78*	7·8
Range	0·9–3·5	0·9–10·5	2·8–9·5	5·1–10·7

*$P<0{\cdot}05$, †$P<0{\cdot}01$, *versus* group 3 (developed metastases), Wilcoxon rank sum test

NORs were significantly increased in malignant prostatic tissue compared to benign. NORs were significantly increased in patients destined to develop metastases and may be useful as predictors of disease outcome

Does flow cytometry accurately determine tumour ploidy?

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More recent studies of ploidy analysed by flow cytometry in breast cancer have failed to confirm earlier findings relating ploidy determined by static cytometry to prognosis[1]. A recent comparison of ploidy determined by flow and static cytometry in papillary thyroid cancer showed that only aneuploidy determined by the latter technique was of prognostic significance[2]. To clarify this we have investigated possible insensitivity of flow cytometry to aneuploid events in breast cancer by simultaneous static and flow cytometric analysis

Cell suspensions obtained by enzymatic disaggregation of 65 breast cancers were stained by the Schiff reagent or diaminodio-2-phenyl indol-dichloride (DAPI) and their cellular DNA content measured by microdensitometry and flow cytometry respectively.

		Static cytometry		
		Aneuploid	Diploid	Total
Flow cytometry	Aneuploid	31	—	31
	Diploid	16	18	34
	Total	47	18	65

While all lesions defined as aneuploid by flow cytometry were confirmed by static cytometry, 16 of 34 lesions identified as diploid were found to be aneuploid.

In breast cancer, as in thyroid cancer, flow cytometry is insensitive in the assessment of aneuploidy which could explain discrepancies between published studies. To correct this problem microdensitometry should be performed on all samples defined as diploid by flow cytometry.

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Tissue oximetry—monitoring of acute ischaemia in free tissue transplants and of graded limb ischaemia

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Peripheral tissue perfusion is important in surgical patients. However, its measurement is difficult in clinical practice. Subcutaneous oximetry (PscO$_2$) seems capable of quantifying peripheral perfusion[1]. This investigation was undertaken to study the sensitivity of tissue oximetry (TO) during graded limb ischaemia and during occlusion of the vascular supply to a free tissue transplant TO was determined by an unheated needle electrode placed in an implanted Silastic® tonometer[2]. In seven pigs (group I) PscO$_2$ was registered in the anterior tibial region. The aortic blood flow was measured continuously and collateral circulation to the hindlimb was occluded. PscO$_2$ was registered after reducing the aortic blood flow to 10 per cent of the initial value and during controlled blood flow increment. In six pigs (group II) a latissimus dorsi myocutaneous island flap and in two pigs a cutaneous buttock island flap were raised. PscO$_2$ and muscular oxygen tension (PmO$_2$) in the island flaps were registered during occlusion of the supplying artery.

In group I, PscO$_2$ decreased to 47 ± 5 per cent (mean ± s.e m.) of the initial PscO$_2$ and increased non-linearly with increasing blood flow PscO$_2$ was significantly reduced until blood flow had reached 50 per cent of the original value. In group II, PscO$_2$ in the latissimus dorsi flap and the buttock flap and PmO$_2$ in the latissimus dorsi flap were significantly reduced after 15 min occlusion and reached a minimum level of 30 ± 9 per cent, 34 ± 6 per cent and 28 ± 5 per cent of the original values respectively.

Tissue oximetry seems capable of identifying and quantifying acute vascular catastrophes and since the method is simple and minimally invasive, it has promise of clinical application.

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Effects of nitroprusside on spinal cord perfusion pressure during aortic cross-clamping

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Nitroprusside (NTP) is commonly used to control proximal blood pressure (p-BP) during aortic cross-clamping (AXC) We investigated the effects of NTP on spinal cord perfusion pressure (SCPP), spinal cord blood flow (SCBF) and paraplegia rate. Somatosensory evoked potentials (SEP) were monitored in 12 dogs who had AXCs placed for 30 min. SCPP was determined as: distal aortic pressure (d-BP) minus CSF pressure (CSF-P). SCBF was measured using microspheres. In the experimental group ($n=6$), NTP was used to lower the p-BP to 100 mmHg. SEP changes were quantitated as the time to SEP loss Neurological injury was graded from 0 to 4 using Tarlov's criteria (0 = spastic, 4 = normal).

	Neurological injury	d-BP (mmHg)	CSF-P (mmHg)	SCPP (mmHg)	SCBF (ml 100 g^{-1} min^{-1})	SEP loss (min)
Control	0/6	24·7	12·8	12·7	10·18	11·01
NTP	6/6*	10·5†	20·4†	−9·8†	5·03 (n.s.)	3·32†

*$P<0{\cdot}05$ Fisher's exact test, †$P<0{\cdot}05$ Student's *t* test

NTP significantly reduces d-BP, increases CSF pressure, and consequently reduces the SCPP. These changes are associated with earlier SEP loss and a lower Tarlov's grade. Differences in SCBF could not be documented by microspheres owing to inaccuracies of this technique at low flows. These data confirm earlier reports cautioning against use of NTP during AXC and elucidate the mechanism of spinal cord ischaemia when using this agent. We advocate the use of mechanical unloading instead of NTP for control of p-BP during AXC.

Transcutaneous oxygen pressure index as an indicator of amputation wound healing

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Transcutaneous oxygen pressure measurement ($TcpO_2$) has been used to try to predict amputation wound healing in patients with peripheral arterial occlusive disease (PAOD). A wide range of values has been given, above which wound healing will occur. This study examines the use of a $TcpO_2$ index (the ratio of the limb to trunk $TcpO_2$) to predict amputation wound healing.

Sixty-three patients with PAOD requiring lower limb amputation were studied. Pre-operative $TcpO_2$ measurements were made on the anterior chest wall, mid-dorsum of the foot, 10 cm below the knee anteriorly and 10 cm above the knee anteriorly. This information was not available to the surgeon who selected the amputation site on clinical criteria. Wound healing was successful if healed in 4 weeks, delayed if healed in more than 4 weeks, and failed if further surgery was required.

Twenty-nine wounds failed to heal, and all had a $TcpO_2$ index of less than 0·66. The thirty-four amputations that healed all had an index greater than 0·7. The absolute $TcpO_2$ values failed to predict healing in eight patients whose $TcpO_2$ values ranged between 31 and 34 mmHg. Of these, six failed to heal and two had delayed healing.

The $TcpO_2$ index can predict amputation wound healing and is a more discriminatory test than absolute $TcpO_2$ measurement.

Does weight influence claudication distance?

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Conservative measures to improve claudication distance include advice on smoking, exercise, diet and weight reduction[1]. Although effects of smoking, exercise and diet are established, the effect of weight on claudication is less clear. This work studies the effect on stable claudicants of carrying extra weights.

Twenty stable claudicants were exercised on a treadmill (3·5 km/h, 0 per cent slope) carrying 0, 2·5, 5, 7·5 and 10 kg weights in randomized sequence. Maximum claudication distance (CD) and ankle–brachial pressure indices were recorded. Height, weight and ideal weight were recorded and patients categorized into mild (CD > 200 m) and severe (CD < 200 m) claudicants. Response index (RI) was calculated as reduction in distance walked per kilogram load.

$$\left(\mathrm{RI} = \frac{\mathrm{CD}\ (0\text{–}10)}{10}\ \mathrm{m/kg}\right)$$

Claudication distance was reduced in subjects carrying 5 kg or more ($P < 0·01$). A linear relationship was demonstrated between mean claudication distance and load carried ($r = 0·98$; $P < 0·01$) with a response index of 10·2 m/kg. The RI of 26·1 ± 9·5 m/kg in mild claudicants was greater than the 3·4 ± 0·8 m/kg observed in severe claudicants ($P < 0·01$).

	Claudication distance (m)					
	Load (kg)					RI
Group	0	2·5	5	7·5	10	(m/kg)
All	249	231	206	158	147	10·2
	±61	±58	±51†	±36†	±36†	±3·6
Severe	112	108	102	85	79	3·4
	±12	±13	±14*	±12*	±11*	±0·8
Moderate	567	518	448	380	308	26·1
	±132	±134	±122*	±82*	±90*	±9·5*

This study demonstrates that extra weight adversely effects claudication distance. For every 1 kg carried the subjects walked 10·2 m less. For mild claudicants this increased to 26·1 m and suggests that weight reduction may deserve greater emphasis in the management of some patients with intermittent claudication.

Statistical analysis: paired Wilcoxon and Mann–Whitney *U* test; all results mean ± s.e.m., *$P < 0·05$, †$P < 0·01$.

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Role of B-mode venous mapping in infra-inguinal arterial bypasses

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Initial experience with B-mode ultrasound vein mapping (B-MAP) has shown its potential in infra-inguinal arterial bypasses[1].

This study presents the long-term follow-up on 328 patients on whom B-MAP was performed over a period of 3 years. In 269 patients, B-MAP indicated there was a suitable vein for an *in situ* bypass and 83 per cent of these patients underwent successful revascularization, with a 1-year patency of 95 per cent. In 29 patients, adequacy of vein size was questionable, despite being continuous from groin to ankle. Of these patients, 19 underwent successful bypass with a 1-year patency rate of 94·3 per cent. B-MAP indicated an unsuitable vein in 30 patients. There was no correlation between vein complexity (double/triple systems) and vein utilization, operability or 1-year patency rates. Where no suitable greater saphenous vein was found, the short saphenous and remaining portions of the greater saphenous vein were mapped thus allowing the performance of composite bypasses and achieving limb salvage in 23 patients. We conclude that B-MAP is the investigation of choice to assess the venous system of the lower extremity preparatory to lower limb revascularization.

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Why do PTFE grafts fail in the first year?

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Polytetrafluoroethylene (PTFE) arterial grafts frequently develop a pseudo-intimal lining and occlude in the months after implantation[1]. We compared early and late graft platelet accumulation in a canine model and investigated their relationship to pseudo-intimal hyperplasia.

Autologous ^{111}In-labelled platelet accumulation, expressed as thrombogenicity index (TI), was measured in femoral PTFE grafts in 40 greyhounds 1 and 8 weeks after implantation. At 8 weeks the grafts were excised, radiolabelled platelet deposition was measured and percentage luminal narrowing by pseudo-intima was calculated by grid microscopy.

Mean (± s.e.m.) early postoperative TI of 0·05 ± 0·02 doubled by week 8 to 0·11 ± 0·02 ($P < 0·05$). In the 12 grafts which developed occlusion or stenosis greater than 50 per cent, initial TI was 0·14 ± 0·05 compared with only 0·03 ± 0·12 in 28 widely patent grafts ($P < 0·05$). TI at 8 weeks correlated closely ($r = 0·81$) with radiolabelled platelet deposition on the excised graft of 0·012 ± 0·003 per cent of injected activity ($P < 0·001$). Both early and late TI were strongly related to pseudo-intimal thickening with $r = 0·51$ ($P < 0·01$) and $r = 0·63$ ($P < 0·02$) respectively.

These data demonstrate increasing luminal platelet deposition with time which suggests that established pseudo-intima may be more thrombogenic than graft surface. This process may promote progressive pseudo-intimal growth and could explain the high graft failure rate in the months after surgery.

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Mechanisms of aneurysm formation distal to synthetic vascular graft: clinical facts and their theoretical explanations

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The effects of either bypass or replacement grafting of the long segment of aorta or large arteries by using a synthetic vascular prosthesis on the cardiovascular system have been investigated by the authors with new findings[1]. Hypertrophy of the left ventricle and accentuated pulse pressure in the immediate distal artery were the most outstanding effects after surgery.

Recently we had two patients who developed acute (developed within 3 h on the 5th postoperative day) and chronic (2 months postoperatively) aneurysm respectively simultaneously at the bilateral femoral arteries several centimetres distal to the *Y*-grafts of abdominal aorta to iliac arteries

One of the causes of these phenomena was thought to be a lack of 'Windkessel' and compliance properties of the vascular graft with long length and thick diameter.

Theoretical explanations could be attempted by some principles and hypotheses of poststenotic dilatation, Laplace law, elastic mismatching, augmented peaking and steepening of arterial pressure waves and other pathological factors from not only the surgical aspect but also from haemodynamic, rheological and multidisciplinary aspects.

1 Maeta H, Hori M. Effects of a lack of aortic 'Windkessel' properties on the left ventricle. *Jap Circul J* 1985, **49** 232–7

Cost-effectiveness of intra-arterial thrombolytic therapy

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Medical costs were determined for 23 patients (18 men, 5 women, aged 33–86 years) who received 24 intra-arterial thrombolytic infusions during 1984–1986, 14 arteries and 10 bypass grafts were treated after occlusion by primary thrombosis (22) or embolism (2) Time from symptom onset to treatment was 1–28 days (mean, 11 days) Streptokinase (5000 units/h, mean 33 h duration) was employed in 8 cases, and urokinase (100 000 units/h, mean 34 h duration) in 16 cases This treatment resulted in complete success (thrombolysis eliminated symptoms without surgery) in 5 cases (21 per cent), partial success (thrombolysis aided, limited or postponed subsequent surgery) in 7 cases (29 per cent); failure (no thrombolysis or clinical change) in 6 cases (25 per cent); and complications (deterioration required urgent operation) in 6 cases (25 per cent)

Of the 19 patients without 'complete success' after thrombolytic therapy, 16 required surgery during the same admission; 2 were not operable due to distal disease, and 1 declined operation Of the 16 operations, 15 were successful (graft or artery patency restored with limb salvage), while 1 failed All 12 patients whose thrombolytic treatment resulted in 'failure' or 'complication' underwent successful surgical treatment during that hospitalization.

Total cost of thrombolytic treatment averaged $8200 per infusion ($n=24$) and was comparable to the cost of surgical treatment ($8900 per patient in the 16 patients who required operation despite thrombolytic treatment) The effective cost per complete success of thrombolytic therapy was $39 600, and per complete or partial success was $16 500 (cost of all cases divided by number of successful cases). This was significantly more than the effective cost of $9500 per complete success of surgical therapy ($P<0·01$). Although intra-arterial thrombolytic therapy is effective in certain cases, better patient selection criteria must be developed to improve its cost-effectiveness

Premixed food with cyclosporin A (CyA) and glucose tolerance test (GTT) alteration in the rat

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Intraperitoneal injection or stomach tube administration of cyclosporin A (CyA) are time-consuming methods. The stress factor is another side-effect of these methods. The aim of this work was to examine a new method of CyA administration to rats. The effect of different CyA blood concentrations on the pancreatic islet cell function was also studied.

Thirty female Wistar rats weighing 220–250 g were divided into three groups Group A· food equivalent to 5 mg/kg bodyweight CyA, group B: 10 mg/kg bodyweight CyA, and group C. 20 mg/kg bodyweight CyA. The food granules premixed with CyA (supplied by Sandoz, Basel) and water were given *ad liberum*. Food and animals were weighed twice weekly. Mean food uptake was 16 g daily in all groups Blood samples were collected before food, 1, 3, 7, 28 and 56 days after onset of food administration for blood CyA concentration. Before killing (day 56) GTT was performed. Specimens of heart, lung, spleen, liver, kidney and pancreas were taken for histological evaluation.

All animals accepted the food premixed with CyA very well No loss of bodyweight occurred during the observation period of 56 days

	CyA level				
Group	day 1 (ng/ml)	day 3 (ng/ml)	day 7 (ng/ml)	day 28 (ng/ml)	day 56 (ng/ml)
A	96·6 (±40)	165 (±24)	102 (±25)	202 (±60)*	161 (±41)
B	295 (±99)	344 (±158)	485 (±107)	831 (±207)†	365 (±216)
C	725 (±362)	1041 (±526)	1999 (±417)	3130 (±372)‡	3193 (±266)

Values are mean ± s.e.m ; *$P<0·025$, †$P<0·005$, ‡$P=$n.s.

The CyA concentration in blood for groups A and B increased from day 1 until day 28. For group C there is no decrease after day 28 Groups A and B show a significant drop of mean CyA concentration after 28 days with unchanged food intake. GTT after 56 days of CyA premixed food intake follows

	Glucose level			
Group	0 min (mmol/l)	10 min (mmol/l)	120 min (mmol/l)	K value
A	4·48(±1·4)	16·44(±3)	5·78(±3)	1·01
B	6·31(±1·3)	13·57(±2·5)	11·11(±4·9)	0·22
C	13·73(±5·2)	23·27(±4·2)	20·20(±8)	0·062

Values are mean ± s.e.m

All rats of groups B and C were diabetic at the end of the observation period. Histological examination of the pancreas revealed vacuolization of islet cells in animals with high CyA concentration.

The food premixed with CyA is an excellent method of administration and for study of CyA effects in rats, without stress for the animals The toxic effects of high CyA blood concentration on the pancreatic islet cells is confirmed.

Urinary amylase and immunoreactive metabolites of thromboxane B_2 (TxB_2) and 6-keto-prostaglandin $F_{1\alpha}$ ($6kPgF_{1\alpha}$) in rat pancreatic allograft rejection

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Pancreas transplants were performed in acute streptozotocin-diabetic young male rats, with urinary tract exocrine drainage Twenty-four hour urines were collected, into indomethacin, before diabetes, pre-operatively, and daily from the second postoperative day The urine was frozen and later assayed for TxB_2 and $6kPgF_{1\alpha}$ by radioimmunoassay, and for amylase activity. Daily testing for glycosuria and alternate day serum chemistry was performed. Five isografts ($RT1^{d}$) and five allografts ($RT1^{a}$ into $RT1^{u*1}$) were followed for 9 days Results were analysed by Student's *t* test. Glycosuria returned on day 7 in one allograft and on day 8 in the other four. Serum glucose differentiated the groups only on day 9 ($P<0·01$) By day 7, allografts passed significantly more urine (ml 20·2 ± 4·4 *versus* 12·0 ± 2·4, $P<0·01$) and their urinary amylase output was significantly decreased (log U/24 h. 2·14 ± 0·42 *versus* 3·66 ± 7·72, $P<0·01$). $6kPgF_{1\alpha}$ was raised from the sixth post-transplant day (pmol/24 h 519 ± 37 *versus* 292 ± 90, $P<0·001$) and TxB_2 on the fourth (49·8 ± 3·9 *versus* 40·9 ± 1·7, $P<0·002$), fifth

($71{\cdot}9\pm13{\cdot}6$ *versus* $53{\cdot}0\pm9{\cdot}2$, $P<0{\cdot}05$) and seventh ($98{\cdot}3\pm15{\cdot}8$ *versus* $50{\cdot}5\pm10{\cdot}6$, $P<0{\cdot}001$) days after transplantation. A significant rise in urinary immunoreactive prostanoids precedes the fall in urinary amylase making it worthy of further evaluation in early diagnosis of acute rejection in vascularized whole organ pancreas transplantation.

Distal femoral osteo-articular allografts in rats

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The repair of damaged articular cartilage continues to present a challenge and has prompted practical experiments exploring types and sources of transplants There are several advantages to using allografts as opposed to autografts To begin with, there is a certain amount of morbidity associated with the harvest of any autograft, in addition to the fact that sufficient autograft material might not always be available. Forty femoral condyles were harvested initially from ten rats. There were two groups. (a) control autograft group ($n=20$) (Lewis/Lewis), (b) allograft group, twenty Lewis rats served as the recipient animals and Brown Norway provided the twenty donor allografts In this group ten rats (b-2) received glycerolized allografts frozen at 2°C to −60°C and then transferred into liquid nitrogen freezers and maintained in the vapour phase of liquid nitrogen A 2–3 mm section of femoral joint surface was removed and replaced with appropriately trimmed allografts that were securely fixed in place with Kirschner's wires There were no clinical differences between the two groups. In group (a) nuclear morphology appeared to be normal while many empty lacunae were seen in group (b) The histological appearance of chondrocytes showed more normal appearing cells in group (a). At 9 weeks, histologically, bony union was present in all grafts However, group b-1 had microscopic resorption of subchondral bone. At 12 weeks group b-2 continued to look grossly intact Histologically, the graft bone trabeculae were well incorporated The cartilage morphology was well preserved with continued uptake of mucopolysaccharide stain

The groups were similar in retaining their structures through 6 weeks However, by 9 weeks, group b-1 showed significant resorption of subchondral bone with contracted fibrocartilage replacing articular cartilage These results warrant further investigation of frozen preserved osteochondral allografts

Transplantation of the thymus in immunodeficient diabetes-prone BB rats

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The spontaneously diabetic BB rat constitutes the best animal model for human type I diabetes mellitus (DM) DM can be prevented in the BB rat by a variety of immunotherapeutic interventions, including transplantation of unfractionated MHC-compatible bone marrow or by administration of antilymphocyte serum or cyclosporin, suggesting that beta cell destruction is the result of an immune-mediated process Since the T cell matures and is educated to self in the thymus, a defect in thymic differentiation of T cells in immunodeficient BB rats is hypothesized. To evaluate this possibility, we transplanted irradiated neonatal Wistar Furth (WF, MHC-compatible) thymuses to the renal subcapsule of 4–5-week-old diabetes-prone BB rats (BBdp) that had been rendered immunologically tolerant to WF antigens (to prevent rejection)

Group	Incidence of diabetes (No diabetic/total (%))	Age at onset
BBdp controls	22/52 (42·3)	95 ± 6
BBdp tolerant WF	23/54 (42·6)	98 ± 7
BBdp tolerant WF+ WF thymus	22/50 (44·0)	85 ± 4

These results demonstrate that transplantation of a WF thymus has no effect on the incidence or age at onset of diabetes in BB rats FACS analysis of lymphocyte subsets in recipients of thymus transplants demonstrated a persistent profile of T cell immunodeficiency We conclude that defective lymphocyte maturation and the failure to down-regulate autoimmune destruction of beta cells in the BB rat is secondary to a genetically determined germ-line defect and is not a consequence of a defective thymus maturation

Contribution of interstitial Ia$^+$ cells to the immunogenicity of rat fetal pancreas allografts

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Fetal pancreas allografts are of potential value in the treatment of diabetes but their use is hampered by their particular susceptibility to rejection. This study examines the contribution of interstitial Ia$^+$ cells to the immunogenicity of rat fetal pancreas allografts by transplanting fetal pancreas in which the original donor strain Ia$^+$ interstitial cells have been eliminated by a period of residence in an intermediate host. DA fetal pancreas was transplanted into the renal subcapsular site of either PVG recipients receiving cyclosporin A (15 mg kg^{-1} day^{-1}) ($n=5$) or congenitally athymic PVG rnu/rnu recipients ($n=5$) After 35 days, the recipient PVG kidney, along with the non-rejected fetal pancreas allograft, was transplanted into a fresh unmodified PVG host. Immunohistological analysis of the pancreas at the time of transplantation confirmed the absence of donor strain Ia$^+$ interstitial cells However, serial examination of the fetal pancreas allograft after retransplantation showed rapid immunological rejection with complete graft destruction by day 14 in all animals. These results indicate that passenger leukocytes do not appear to be the only important immunogen influencing rat fetal pancreas allograft survival, and suggest that strategies of immunomodulation which depend on the elimination of passenger leukocytes may be ineffective in fetal pancreas transplantation

Peripheral composite tissue allografts (CTA) in limb transplantation in rats

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The rat limb allograft serves as an excellent experimental model for CTA Allografts of composite tissue have the promise of repairing major anatomical defects. The purposes of this investigation were: (a) to study the experimental grafting of a rat's limb; (b) to determine the length of survival with or without the use of cyclosporin A (CyA) and to examine the pathogenesis of limb rejection; (c) to select biochemical parameters that could be used for routinely assessing the performance of the CTA, and (d) to evaluate the risks and benefits of continuous immunosuppressive treatment using CyA Seventy-nine Lewis rats (weight 286 ± 35 g) each receiving an orthotopic transplant of a LEW Brown Norway (weight 267 ± 56 g) hind limb were evaluated CyA, 10 mg kg^{-1} day^{-1} was administered subcutaneously after surgery, and each day for various lengths of time in 39 rats (control, $n=40$) Mean survival times were approximately 10·5 times greater in rats treated with CyA On the 7th day after transplantation a significant decrease of ATP ($3{\cdot}7\pm0{\cdot}5$ µmol g^{-1} wet weight of muscle, $P<0{\cdot}001$) appeared. On the 21st day a significant multiple correlation between FN BGP and ATP ($r=0{\cdot}726$, $P<0{\cdot}01$) was seen in the group without CyA The histological studies for the allogenic vascularized limb grafts showed that neutrophils and lymphocytes had invaded the marrow. It is clear that CyA has the capability in the rat model to prolong composite tissue grafts with virtually no sign of rejection across a complete major histocompatibility barrier when treated continuously. The reason for the low adenine nucleotides in transplanted muscle is thought to be primarily an increased formation and deamination of adenosine monophosphate during hypoxia.

Orthotopic rat liver transplantation: changes in arachidonic acid metabolites during acute rejection

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Increases in thromboxane A_2 (TX A_2) and prostaglandin I_2 (PGI_2) have been linked to heart and kidney allograft rejection In the rejecting liver the inflammatory cells and Küpffer cells might also produce eicosanoids. We have therefore undertaken in a rat strain combination which constantly rejects liver grafts (DA-LEW) ($n=11$) to identify the production of TxA_2, PGE_2 and PGI_2. This has been assessed on alternate days by the urinary excretion of their metabolites (2,3 dinor TxB_2, PGE_2 and 6-keto-$PGF_{1\alpha}$ respectively). Mean rat survival was $11\pm1{\cdot}67$ s e m days

Liver function was monitored by measuring plasma bilirubin, alkaline phosphatases and transaminases. Acute rejection was confirmed histologically. During rejection the excretion of 2,3 dinor TxB_2 increased to a maximum between day 7 and 11: mean highest value (m.h.v.) = 743·14 ± 165·7 μg/g creatinine (*versus* 3·7 ± 0·28 at day 0), then decreased. 6-Keto-$PGF_{1\alpha}$ and PGE_2 excretion increased more moderately (m.h.v. = 81·07 ± 23·63 *versus* 3·73 ± 0·77 at day 0; and 45·71 ± 9·25 *versus* 3·93 ± 0·83 at day 0 respectively). No major change was seen in a control group (DA-DA liver transplantation). Our present results documenting an increased synthesis of TxA_2 and to a lesser extent of PGI_2 and PGE_2 suggest that the measurement of their urinary metabolites could be useful in the detection of acute liver allograft rejection.

Fine needle aspiration biopsy in acute rejection and infection in liver transplant patients

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Fine needle aspiration biopsy (FNAB) has proved to be of great value in detecting acute rejection of liver transplants both in experimental and clinical studies. The results have also been correlated to histology. In FNAB the immunological inflammatory events of the graft are compared with those of a corresponding blood specimen. The intensity of inflammation differentiation between the graft and the blood is numerically expressed as total corrected increment (TCI). A low TCI indicates a normal state. As infection and acute rejection are difficult to distinguish from each other in liver transplant patients we compared prospectively these two events in 19 consecutive liver transplant patients. A total of 323 FNAB specimens were analysed. Results are mean ± s.e.m.

Acute rejection occurred 16 times and infection 22 times. Onset of acute rejection resulted in significantly higher TCI values than onset of infection ($P<0{\cdot}001$). During ongoing infection no changes were seen in the FNAB. Cytomegalovirus infection caused some overlapping between groups.

	Acute rejection onset ($n=16$)	Infection onset ($n=22$)	Infection course ($n=64$)
TCI	6·43 ± 0·87	1·59 ± 0·24	1·76 ± 0·20

We conclude that onset of acute rejection may be differentiated from onset of infection by the FNAB method in liver transplant patients. The course of infection resulted in similar findings to the onset of infection.

Azelaic acid: a possible substrate in total parenteral nutrition

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Experimental evidence suggests a possible use of the medium chain dicarboxylic fatty acids (MCDFA) as energy substrates in total parenteral nutrition. We have compared the different response to MCDFA *versus* intralipid (IL). Among MCDFA we have chosen C9 azelaic acid (AA) because it has already been safely used in humans. To investigate metabolic effects of AA *versus* IL administration, 10 g AA was infused intravenously, over 80 min to six overnight fasting healthy volunteers; four of them received, as control, 10 g IL administered with the same modality. AA, measured by gas liquid chromatography from the beginning of the infusion for 240 min, reached a peak concentration at 80 min (589 ± 60·6 μg ml^{-1}) and was rapidly cleared from plasma (82·3 ± 5·2 μg ml^{-1} at 240 min). Simultaneously respiratory and metabolic variations were detected by indirect calorimetry. In both groups the CO_2 production remained essentially unchanged throughout the experiment. The O_2 consumption increased over basal values, reaching a peak at the end of the infusion in both groups. Respiratory quotient consequently decreased significantly ($P<0{\cdot}05$; AA from 0·85 ± 0·06 to 0·77 ± 0·06; IL from 0·89 ± 0·06 to 0·77 ± 0·04) and the lipid oxidation rate increased during and after the infusion ($P<0{\cdot}05$). Metabolic rate (kcal h^{-1} m^{-2}) showed a slight increase (AA from 34·2 ± 4·4 to 41·7 ± 6·7, IL from 35·9 ± 5·1 to 43·5 ± 9·4) during the infusion and remained sustained for the entire study period. There was no statistically significant difference between AA and IL treatment. Our data suggest that AA has been oxidized to produce energy, with a metabolic behaviour identical to IL. The metabolic effect was even more striking if one considers that the caloric equivalent of AA is only 5 kcal g^{-1} compared with the 9 kcal g^{-1} of IL.

Effect of reduced oxygen delivery on function in the isolated rat kidney

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The kidney is a heterogeneous assembly of glomeruli and tubules whose interaction during diminished O_2 delivery is not well understood. This study used isolated rat kidneys perfused at 90–100 mmHg pressure and 37°C with a modified Krebs' buffer for 120 min. Oxygen delivery (O_2del, μmol min^{-1} g^{-1}), perfusate flow rate (PFR, ml min^{-1} g^{-1}), glomerular filtration rate (GFR, ml min^{-1} g^{-1}), absolute sodium reabsorption (Na_{ab}, μEq min^{-1} g^{-1}), oxygen consumption (VO_2, μmol min^{-1} g^{-1}), per cent sodium reabsorption (Na %) were measured. After a 30 min baseline period, perfusate oxygen tension (PO_2 mmHg) was reduced from 550 to 50 ($n=6$). Data (mean ± s.e.m.) listed were obtained at the PO_2 at which functional parameters became significantly different from time-matched controls ($n=6$).

	O_2del	PFR	GFR	Na_{ab}	VO_2	Na %
Control	23·0	33·3	0·65	81·9	8·3	96·9
	±1·3	±1·8	±0·05	±7·7	±0·3	±0·3
$PO_2=400$	16·0	33·2	0·42	53·7	6·7	96·2
	±0·6†	±1·1	±0·06*	±8·2*	±0·5*	±1·4
Control	23·2	33·7	0·45	58·3	7·9	96·1
	±1·2	±1·7	±0·02	±2·9	±0·2	±0·6
$PO_2=200$	8·0	33·3	0·21	25·8	4·7	92·4
	±0·6‡	±1·4	±0·04‡	±6·5†	±0·5‡	±1·5*

*$P<0{\cdot}05$, †$P<0{\cdot}01$, ‡$P<0{\cdot}001$

GFR was depressed at a higher PO_2 than Na % and declined parallel with the reduction in O_2del ($r=0{\cdot}844$, $P<0{\cdot}001$). Na_{ab} and VO_2 correlated with the decrease in GFR ($r=0{\cdot}988$, $P<0{\cdot}001$, and $r=0{\cdot}808$, $P<0{\cdot}001$). The data suggest a glomerular mechanism independent of PFR that decreases tubular workload (Na_{ab}) during reduced O_2del. Tubular O_2 dependent function (Na %) is protected relative to GFR.

Comparison between subcutaneous, conjunctival and transcutaneous measured tissue oxygen tension during haemorrhage and resuscitation

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A fundamental effect of hypovolaemic shock is a diminished tissue oxygenation owing to an inadequate tissue perfusion. Measurement of individual tissue oxygen tension provides an ideal guide to the adequacy of oxygen delivery. The aim of this study was (1) to compare the sensitivity of three methods of tissue oxygen measurements, in conjunctiva ($P_{cj}O_2$), on the skin surface ($P_{tc}O_2$) and in subcutis ($P_{sc}O_2$), during haemorrhage and volume substitution, and (2) to assess whether loss of oxygen-carrying capacity can be compensated by restoring the volume depletion with isotonic saline.

Oxygen tensions and central haemodynamic parameters in eight anaesthetized dogs were followed during a controlled stepwise arterial bleeding and resuscitation with equal volumes of isotonic saline. After one step of bleeding $P_{sc}O_2$, cardiac output (CO), mean pulmonary arterial pressure (MPAP) and central venous pressure (CVP) decreased significantly from baseline while $P_{tc}O_2$, $P_{cj}O_2$, mean arterial pressure (MAP) and heart rate (HR) were unchanged. After the last step of bleeding $P_{sc}O_2$, $P_{tc}O_2$ and $P_{cj}O_2$ were decreased by 84 per cent, 82 per cent and 92 per cent respectively. CO, MAP and CVP were decreased by 60 per cent. HR increased by 35 per cent. During infusion the rate of increase was greatest for $P_{cj}O_2$ and smallest for $P_{sc}O_2$. After infusion $P_{tc}O_2$ and $P_{cj}O_2$ reached values above baseline while $P_{sc}O_2$ reached 88 per cent of the baseline value.

It is concluded that oxygen tension monitoring provides a sensitive indication of tissue perfusion Determination of $P_{tc}O_2$ appears to be the most suitable of the three tested methods Even when considerable oxygen-carrying capacity has been lost, a sufficient perfusion can restore the oxygen supply.

Pre-operative intravenous nutrition switches the liver from a gluconeogenic to a synthetic mode

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The burst of hepatic protein 'synthesis' which occurs in response to trauma or sepsis is probably of great importance to immune competence and wound healing In malnourished patients the liver is in a 'gluconeogenic mode' which is suboptimally suited to protein synthesis. The influence of 7 days of pre-operative intravenous nutrition (IVN) upon hepatic carbohydrate stores, key enzyme activity and protein synthetic activity was studied in patients with gastrointestinal cancer who had lost >5 kg in weight

Patients were randomized to receive hospital food only or hospital food and IVN (0·18 gN$_2$ 24 h^{-1}; 126 kJ glucose kg^{-1} 24 h^{-1}) for 7 days before laparotomy. IVN was discontinued 12 h before laparotomy Patients who had not lost weight received hospital food only and formed a control group Wedge biopsies of liver were obtained peroperatively. Glycogen was determined by digestion with hexokinase, activity of the key enzymes phosphofructokinase (PFK) and fructose bisphosphatase by spectrophotometry, and protein synthesis after incubation with ^{14}C-leucine

Patients (n)	Glycogen (mg glucose g^{-1} dry liver)	Protein synthesis (nmol × 10^{-5} h^{-1} mg^{-1} protein)	PFK	Fructose Bis-phosphatase
			(μmol min^{-1} g^{-1} wet liver)	
Control (9)	68·4±24·4	1·05±0·12†	6·40±0·61	6·10±1·28
Food only (10)	52·2±16·4	0·46±0·06	6·46±0·48	5·54±0·67
Food+IVN (10)	163·1±23·7*†	1·44±0·20†	4·34±0·42*†	2·77±0·56*†

Values are mean±s.e.m., $^*P<0{\cdot}01$ *versus* control, $^\dagger P<0{\cdot}01$ *versus* food only, Mann–Whitney U test

In patients with gastrointestinal cancer who had lost weight, hepatic glycogen concentrations were low, protein synthesis was reduced and there were high levels of PFK and fructose bisphosphatase, indicating gluconeogenesis After 7 days of IVN there was reduced gluconeogenesis, increased protein synthesis and larger stores of hepatic glycogen. This may be an important influence of pre-operative IVN.

Release of atrial natriuretic peptide, an endogenous mesenteric vasodilator, in intestinal ischaemia

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Reperfusion of the ischaemic small intestine is accompanied by cardiodepressant effects which contribute to the mortality in intestinal ischaemia Atrial natriuretic peptide (ANP), which is released during cardiac impairment, has numerous actions including mesenteric vasodilatation. The effect of intestinal ischaemia–reperfusion injury on plasma ANP was therefore investigated.

Anaesthetized Wistar rats (groups A and B, $n=6$ in each) were subjected to superior mesenteric artery (SMA) occlusion for 20 min A femoral arterial cannula was used for continuous blood pressure (BP) monitoring and for blood sampling at the end of the ischaemic period (A) or after 5 min reperfusion (B) Six control animals (C) were identically treated but without SMA occlusion A central venous cannula was used for CVP measurements. Plasma ANP was measured by radioimmunoassay. There were no detectable changes in CVP. On reperfusion a significant rise in circulating ANP and a fall in BP were observed but no change occurred during SMA occlusion itself

Group	ANP (fmol/ml)	Blood pressure		
		Basal	Occlusion^a	Reperfusion^b
A	45±7	112±5/76±5	113±5/76±7	101±2/66±2
B	79±12*	113±7/73±4	109±7/69±7	63±5/35±4†
C	36±3	108±8/71±5	104±7/68±4	103±10/69±4

Results are mean±s.e.m.; $^*P<0{\cdot}01$, $^\dagger P<0{\cdot}001$ (*versus* control, ANOVA), or equivalent time points in A (b) and C (a,b)

These results show that intestinal ischaemia–reperfusion injury causes release of ANP which could, via its mesenteric vasodilator action, modulate intestinal blood flow. Furthermore, plasma ANP measurements may be of value in the early detection of cardiac impairment after reperfusion of ischaemic intestine

Attenuation of leucocyte activation during extracorporeal circulation by a new cAMP diphosphoesterase inhibitor

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Activated leucocytes may have an important role in developing complement-related lung injury with pulmonary leucosequestration in the presence of blood–material interaction of the extracorporeal circulation (ECC) in cardiopulmonary bypass and ECMO We evaluated the effects of a new cAMP phosphodiesterase inhibitor (DN) on leucocyte aggregation *in vitro* and the pulmonary leucosequestration during experimental ECC in dogs. The inhibition of DN was assessed in the leucocyte aggregation response induced by leukotriene B$_4$ *in vitro* The animals were divided into two groups: control group ($n=6$) and DN group ($n=4$, DN. 60–80 μg kg^{-1} min^{-1} during ECC) Both groups received the venovenous ECC with a membrane lung for 30 min Arterial leucocyte count (A-WBC) and transpulmonary gradient of WBC (PA-Ao WBC) were measured at 2, 10 and 30 min of ECC

Fifty per cent inhibition of the leucocyte aggregation was obtained at 0·2 μM DN.

		pre-ECC	2 min	10 min	30 min
A-WBC (% pre-ECC)	Control	100	55 ±16*	59 ±23*	41 ±25*
	DN group	100	101 ±41	80 ±37	85 ±25
PA-Ao WBC (mm^{-3})	Control	−175 ±206	+1200 ±330*	+13 ±225	+100 ±470
	DN group	+75 ±386	+125 ±263	+300 ±115	−25 ±150

Values are mean±s.d., *significant difference *versus* pre-ECC value ($P<0{\cdot}05$)

These results suggest that DN prevents the pulmonary leucosequestration induced by ECC with attenuation of the systemic WBC depletion.

Intermittent blood K$^+$ cardioplegia has no advantage over K$^+$ cardioplegia using St. Thomas' Hospital solution or Fluosol

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Some cardiac surgeons prefer blood for cardioplegia because of its buffering capacity, oncotic pressure and O$_2$ transport capacity. Three vehicles for K$^+$-induced cardioplegia were studied under identical conditions using Langendorff-perfused rabbit hearts After 30 min perfusion with Krebs–Henseleit solution (KHS) at 37°C hearts underwent three sequences of 5 min cardioplegic perfusion each, followed by 25 min ischaemia at 27°C Afterwards, the hearts were reperfused for 45 min with KHS at 37°C During reperfusion, systolic pressure (SP, mmHg) and +dp/dt (mmHg/s) were measured at 15, 30 and 45 min. Energy-rich phosphates (ATP, CPr in μmol/g w.w.) were determined in the cardioplegia groups before (BR) and after (AR) reperfusion Carbogen-equilibrated St. Thomas' Hospital solution (S, $n=12$) and Fluosol (F, 10 per cent, $n=12$) as well as oxygenated diluted blood (B, HKT 20 per cent, $n=12$) served as transport media The electrolyte pattern was similar, K^+ was raised to 30 mmol/l. Control hearts (C, $n=6$) were perfused with KHS for 75 (30+45) min at 37°C

	ATP		CPr		15 min		45 min	
	BR	AR	BR	AR	SP	+dp	SP	+dp
C		4·5		9·5	123	1742	123	1675
S	4·0	4·4	4·5	8·4	107	1614	110	1652
B	3·6	3·7*	2·0†	7·8	62*	876*	79*	1122*
F	3·4†	3·5*	5·0	7·0	84*	1047*	94*	1199*

*Significant *versus* C; †significant *versus* S; $P<0·05$ or better

S-treated hearts had a higher content of energy-rich phosphates and a better cardiac performance during reperfusion than B-treated and F-treated hearts. Under these conditions advantages of blood cardioplegia could not be confirmed because the use of St Thomas' Hospital solution resulted in a better myocardial protection in this study

Increased production of oxygen radicals by circulating monocytes in inflammatory bowel disease—evidence of 'activation'

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Monocytes are the circulating precursors of tissue macrophages, which are prominent in the inflammatory infiltrate of Crohn's disease (CD) and ulcerative colitis (UC). Defective phagocyte function has been postulated as important in the aetiology of CD. To investigate this possibility, we have measured monocyte oxygen radical production by luminol-dependent chemiluminescence in patients with CD ($n=20$), UC ($n=17$) and healthy, age-matched controls ($n=14$)

Blood mononuclear cells were isolated by density gradient separation The number of monocytes in each sample was calculated by non-specific esterase staining Oxygen radical production in response to three different stimuli was significantly greater (Mann–Whitney U test) by monocytes from patients with inflammatory bowel disease than from controls Responses to phorbol myristate acetate were. controls 320±51 counts per second/10^6 monocytes (mean±s.e), CD 2263±482 ($P<0·0005$), UC 1599±404 ($P<0·05$); chemotactic peptide, f-methionyl-leucyl-phenylalanine. controls 139±39, CD 594±156 ($P<0·002$), UC 319±100 (n.s.), latex beads. controls 302±57, CD 1796±302 ($P<0·002$), UC 1458±225 ($P<0·0005$). Furthermore, increased chemiluminescence was seen only in monocytes from patients with active disease, the response of monocytes from patients with quiescent disease being similar to controls

Increased production of oxygen radicals by monocytes in inflammatory bowel disease suggests that these cells are circulating in an 'activated' state.

Patients with outlet obstruction constipation also have obstructed urinary flow

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Patients with outlet obstruction constipation (OOC) contract the puborectalis muscle (paradox) on straining at stool[1] These patients may also have symptoms suggestive of obstructed urinary flow.

We performed standard urodynamics in 10 consecutive females with OOC diagnosed on videoproctography and electromyography. Bladder filling was undertaken until the desire to void. Detrusor pressure, peak flow rate, voiding time and residual volume were recorded during voluntary voiding Eight patients had urinary symptoms (frequency, four, nocturia, four, hesitancy, five; incomplete emptying, five; stress incontinence, three). All patients had normal bladder filling profiles

On voiding, the mean detrusor pressure for the patients studied was normal at 53·3±12 cmH_2O (mean±s e) The corresponding peak flow rate was 19·8±6 ml/s compared with 28·6±3 for expected normal controls ($P<0·05$) The mean voiding time was 73±21 s (mean±s.e) for patients with OOC and exceeded the expected normal of 30 s in nine patients The median residual volume was 35 ml (range 0–150).

These results show that patients with OOC have a variable degree of outlet obstruction uropathy This has important implications for the understanding of the pathophysiology of the anterior pelvic floor

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Role of rectal intussusception in the development of anal incontinence

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Faecal incontinence is commonly associated with overt rectal prolapse Rectal intussusception (RI) seen on proctography may be a precursor of rectal prolapse and may therefore be implicated in the aetiology of idiopathic faecal incontinence (IFI). We have investigated this association by studying 39 patients (4 men, 35 women, age 56, 52–66 years, median and interquartile range) with IFI and 28 normal subjects (N) (4 men, 24 women, n.s , age 45, 40–47, $P<0·001$). Anal canal pressures, proctometrogram, anorectal angles and proctography were performed in each subject Statistical analysis was by χ^2 and Mann–Whitney U test.

Nineteen patients with incontinence had a RI compared with one control subject ($P<0·01$). The IFI patients had significantly widened angles at rest (109, 90–128 degrees; N 84, 78–90, $P<0·001$), and on straining (130, 102–150, N 104, 95–108, $P=0·006$) and reduced basal (45, 26–55 cmH_2O; N 88, 62–99, $P<0·001$) and squeeze (55, 30–100; N 90, 60–148, $P<0·004$) anal canal pressures

	IFI, no RI	*P* (IFI, no RI *versus* control)	IFI+RI	*P* (IFI+RI *versus* control)	*P* (IFI+RI *versus* IFI, no RI)
Resting angle	97, 81–116	n s	120, 100–133	<0·05	<0·05
Straining angle	112, 88–129	n s	150, 130–161	<0·05	<0·05
Min perceived vol (ml)	100, 63–120	<0·001	59, 50–85	0·002	<0·05
Max basal pressure	50, 32–70	<0·001	40, 26–50	0·001	n s
Max squeeze pressure	46, 16–100	0·002	55, 35–90	0·023	n s

The IFI patients with an RI, however, had significantly wider anorectal angles than those patients without RI and control subjects The minimum perceived volume was also significantly reduced in the presence of an RI, explaining why these patients may suffer from frequency and urgency.

These findings demonstrate that occult rectal intussusception is an important yet ignored factor in the development of idiopathic faecal incontinence and its correction may be important in the surgical treatment of the disease

Do patients with haemorrhoids have pelvic floor denervation?

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Straining at stool is found in patients with haemorrhoids, rectal prolapse and faecal incontinence. In the latter two conditions perineal descent and pudendal neuropathy occur. We have carried out anal manometry, measurement of perineal descent, pudendal nerve terminal motor latency (PNTML) and single fibre electromyography (EMG) in the external anal sphincter in 16 patients with haemorrhoids and 20 matched controls to test whether patients with haemorrhoids have denervation of the pelvic floor musculature.

There was no significant difference between the patients with haemorrhoids and controls in resting anal pressure (68±19 (s d) and 63±15 cmH_2O respectively) or voluntary contraction pressure (106±92 and 87±23 cmH_2O). Slow waves were present in nine patients and eleven controls, and ultra-slow waves in five patients and four controls (n s.). There was a significant difference between the patient and control groups in the perineal position at rest (1·2±1·0 cm and 1 7±0 5 cm, $P<0{\cdot}025$) and on straining (−0·5±1 3 cm and 1 1±0 8 cm, $P<0\,005$) There was no significant difference in PNTML between patients and controls (2·0±0 4 ms and 1·8±0 2 ms, $P=0\,07$) but there was a significant difference in the mean fibre density (1 9±0 6 and 1·5±0·2, $P<0\,025$) Eight patients and two controls had raised fibre density (>1·9) ($P=0\,01$) These findings show that patients with haemorrhoids have perineal descent with pudendal neuropathy

Prolonged assessment of anal motility and electromyography (EMG) in patients with prolapsing haemorrhoids

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Anorectal manometric studies in the traditional left lateral position show high anal canal pressures and ultra-slow wave activity in patients with haemorrhoids. To further assess anorectal motility in this condition we studied 6 subjects with prolapsing haemorrhoids and 14 controls using a fine pressure probe (Gaeltec Ltd, OD 2 mm) to assess anorectal motility and silver–silver chloride surface electrodes to record external sphincter activity. Studies were recorded in each ambulant subject over a prolonged period (mean 19 h)

Marked spontaneous reductions in anal canal pressure (sampling reflex equivalents) occurred at rates of 12·9±1 9/h (mean±s e m) during daytime activity in the haemorrhoid group compared with 7 4±2 0/h in controls ($P<0\,05$) These periods of frequent sampling were associated with intense activity in the external sphincter EMG recording in those with haemorrhoids. Mean resting sphincter pressure did not vary significantly with time in individual subjects in either group Rectal contractile events occurred at rates of 2–3/min every 60–90 min in both groups. These data, recorded in a prolonged physiological setting, show that persistent lowering of resting sphincter tone in association with prolapsing haemorrhoids is accompanied by much increased activity in the external sphincter. The latter may account for many of the symptoms of pain and tissue oedema in this condition

Anorectal physiology validated: a repeatability study of the motor and sensory tests of anorectal function

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Sixteen subjects (mean age 50 7±12 8 years, three men) were studied on two separate occasions by two independent investigators in random order with anatomical, manometric and electrophysiological assessment of anorectal motor and sensory function. There was no significant difference between the results obtained by the two investigators in the six separate tests of anorectal function Bias between investigators, 95 per cent confidence intervals (CI) of the bias ±2 s d (limits of agreement) and the average range of values by both methods are given in the *Table*

	Bias	95% CI	±2 s d	Average range
Perineal descent (cm)	−0·07	−0 47 to 0 31	±1 3	0 5–2 4
Anal canal length (cm)	−0·1	−0·2 to 0 4	±1 0	2–4
Resting pressure (cmH_2O)	−10	−25 to 4 7	±42	30–130
Squeeze pressure (cmH_2O)	−9	−32 to 14	±65	40–250
Pudendal nerve				
Latency (ms)	0 1	−0·3 to 0 2	±0 6	1 7–2 7
Fibre density	0 26	−0·04 to 0 57	±0·35	1 83–2 58
Mucosal electro-sensitivity (mA)	0·5	−3 3 to 4 3	±19 0	1 75–23 6

Repeatability for the calculation of fibre density derived from single muscle fibre electromyography (EMG) was assessed with each investigator analysing the other's tracings blind, and showed no significant difference· bias −0 003, −0 07 to 0 06, 95 per cent CI.

In this study the standard tests of anorectal sensorimotor function show a high degree of repeatability between different investigators These tests are validated and allow comparison of data obtained in different centres employing the same techniques

Anal manometry and pouch compliance measurements before ileostomy closure are related to functional outcome of the ileal pouch–anal anastomosis

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After ileal pouch–anal anastomosis (IPAA) but before ileostomy closure, 104 patients underwent anal manometry (anal canal length, mean and maximum resting and squeeze pressures) and pouch capacity and compliance measurements. At the end of 1 year's follow-up (median 438 days) functional outcome for all patients was assessed in terms of stool frequency (day/night), incontinence (day/night), the use of pads, the need for constipating medication and the presence of peri-anal irritation

Patients who complained of night-time incontinence had significantly lower anal resting pressures before ileostomy closure (median 39 mmHg *versus* mean 47 mmHg, $P<0\,05$) than patients who were fully continent at night

Similarly patients who reported the need for constipating agents at the end of 1 year's follow-up also tended to have lower anal resting pressures before ileostomy closure (median 38 mmHg *versus* 46 mmHg, $P=0\,08$) than patients who did not need this medication.

Median pouch compliance, measured before ileostomy closure, was significantly lower in patients with two or more stools at night (1 8 ml/mmHg *versus* 2 3 ml/mmHg, $P<0{\cdot}05$) than in patients with only one or no stools at night.

Anal canal manometric and pouch compliance measurements before ileostomy closure correlate with functional results 1 year after IPAA.

Pitfalls in the diagnosis of breast lesions using fine needle aspiration cytology

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Fine needle aspiration cytology (FNAC) is an accepted diagnostic method in establishing a definite diagnosis of breast cancer However, unsatisfactory and unrepresentative aspirates result in diagnostic failure in some cases In an attempt to define the limitations of FNAC the present study examines the reasons for diagnostic failure in a series of 1200 consecutive aspirates performed between January 1982 and July 1987 Of 184 proven malignancies 152 were diagnosed by FNAC (83 per cent). There were 32 false negative results (17 per cent) There was a high proportion of *in situ* and lobular carcinomas in this group and 10 of 23 invasive carcinomas were <1 cm.

Pathology (total number of cases)	False negatives	% total
Carcinoma *in situ* (3)	3	100%
Lobular carcinoma (12)	6	50%
Invasive carcinoma (165)	23 (tumours <1 cm, $n=10$)	14%
Medullary carcinoma (4)	0	

Of the remaining 13 invasive carcinomas 2 false negative results were attributed to aspirator inexperience and there was no obvious explanation why tumour cells were not obtained in 11 cases Of the 1200 aspirations performed there were only 4 false positive results (0 4 per cent). Three of these were classified as 'suspicious' and one frankly 'malignant' While these results confirm the value of FNAC as a rapid means of diagnosis of breast cancer it is clearly unreliable in patients with *in situ* disease and those with lobular carcinoma. Until a more satisfactory technique becomes available to detect *in situ* and lobular disease FNAC should not replace excision biopsy as a means of diagnosis

Serum thymidine kinase: a tumour marker in advanced breast cancer

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The enzyme thymidine kinase (TK) is associated with DNA synthesis TK serum levels were studied in normal controls, primary breast cancer (PBC) patients and advanced breast cancer (ABC) patients All values are given as picomoles per millilitre per hour

Group	No of patients	Mean value	s.d
Control	20	4·22	1·08
PBC	60	6·22	1·24
ABC	20	9·79	7·56

ABC patients had a significantly elevated serum TK level compared with controls ($P<0{\cdot}01$) and PBC patients ($P<0{\cdot}01$, *t* test)

Twenty PBC patients were followed up after mastectomy by serial 3 monthly TK levels in the disease-free interval Four patients have developed systemic recurrence with a mean serum value of 14·3 pmol $\mathrm{ml}^{-1}\,\mathrm{h}^{-1}$

Ten ABC patients had serial TK levels 2 monthly during the first 6 months of primary hormone therapy External assessment of response to treatment by UICC criteria has been obtained The serum values fell in all five responders (mean 9·12 to 4·78 pmol ml^{-1} h) and rose in all five progressors (mean 8·62 to 38·56 pmol $\mathrm{ml}^{-1}\,\mathrm{h}^{-1}$).

Serum TK reflects stage of disease, being significantly elevated in advanced breast cancer both on serial estimations and in comparison with controls Serial TK levels in ABC patients measures response to systemic therapy.

TK appears to be a useful biochemical marker in breast cancer.

LHRH agonist Zoladex® and anti-oestrogen tamoxifen: a rational combination in premenopausal women with breast cancer?

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In the premenopausal woman the use of Zoladex® (ICI, Macclesfield, UK) results in the production of castrate levels of oestradiol. The combination of Zoladex and tamoxifen has been proposed in the treatment of premenopausal women with breast cancer However, endocrinological assessment is required to show that their combined effects are not antagonistic, since tamoxifen alone stimulates high oestradiol peaks

We have studied 34 patients with oestrogen-receptor positive and negative tumours treated with Zoladex and tamoxifen as initial systemic therapy. Zoladex was given as a monthly subcutaneous injection (3·6 mg) and tamoxifen 20 mg twice daily. Endocrine data were available in 23 patients As with Zoladex alone, patients receiving combined Zoladex and tamoxifen showed transient stimulation of FSH and LH levels over the first 7–10 days (peak mean values 7 units/ml and 14·9 units/ml respectively) with subsequent low gonadotrophin levels (mean <2 units/ml and <1 units/ml respectively). Serum oestradiol and progresterone levels were reduced to castrate levels

There is no endocrinological contraindication to the combined use of Zoladex and tamoxifen in premenopausal women with breast cancer either as adjuvant therapy or in treating advanced disease. One advantage of Zoladex over surgical oophorectomy, particularly as an adjuvant therapy, is that the castration effects are reversible on stopping Zoladex therapy

A prognostic index in radical excision and omental transposition for locally advanced and recurrent breast cancer

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Extensive chest wall disease is a distressing manifestation of breast cancer Radical excision followed by reconstruction using transposed omentum can occasionally result in prolonged palliation However, a few patients quickly develop troublesome recurrent disease adjacent to the omental graft In order to improve patient selection, a 'prognostic index' has been derived using data from 37 patients.

Surgery was deemed inappropriate in 12 patients as further local recurrence appeared within 2 months of omental transfer. In this group, all deaths resulted from progressive locoregional disease. On multivariate analysis (GLIM), 5 of 16 factors studied were independently associated with early recurrence.

t, short interval from initial cancer diagnosis ($P<0{\cdot}001$)
r, previous radioresistance ($P<0{\cdot}001$)
u, area of skin ulceration ($P=0{\cdot}002$)
s, satellite cutaneous deposits ($P<0{\cdot}025$)
m, absence of overt distant metastases ($P=0{\cdot}025$)

Using these criteria, a formula was constructed that accurately categorized 34 of the 37 patients

$$\log_e \frac{P}{1-P} = -26{\cdot}27 + 0{\cdot}068(\mathrm{t}) - 20{\cdot}93(\mathrm{r}) - 0{\cdot}053(\mathrm{u}) - 3{\cdot}54(\mathrm{s}) - 8{\cdot}86(\mathrm{m})$$

Rapid recurrence after omental transposition reflects biologically aggressive breast cancer and the technique is probably not worthwhile when applied to this type of disease. Palliative surgery should not necessarily be dismissed because of the presence of distant metastases

Can monoclonal antibody B72.3 increase the sensitivity of fine needle aspiration cytology?

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Fine needle aspiration cytology (FNAC) is a useful diagnostic technique in palpable breast disease Monoclonal antibody (MAb) B72.3 is directed against a membrane protein of human breast cancer[1]

In a prospective study, 58 consecutive patients with palpable breast disease underwent FNAC The slides prepared by conventional Papanicolaou stain and MAb B72·3 were examined by independent pathologists Histology of the excised specimen showed that 28 had malignant and 30 had benign disease.

	Papanicolaou alone	MAb B72·3 alone	Papanicolaou +MAb B72·3
Sensitivity (%)	82	89	96
Specificity (%)	100	71	77

The sensitivity of FNAC cytology can be increased by combining MAb B72.3 with Papanicolaou staining, at the expense of a reduction in specificity Four carcinomas, missed on Papanicolaou staining, were correctly diagnosed by the combination. Such an increase in sensitivity may be of importance in FNAC of the small and impalpable lesions (localized by stereotactic or ultrasound methods) detected by a breast screening programme

1 Nuti M, Mottolese M, Viora M, Perrone Donnorso R, Schlom J, Natali PG. Use of monoclonal antibodies to human breast tumour associated antigens in fine needle aspirate cytology *Int J Cancer* 1986, **37**: 493–8.

Postoperative metabolic monitoring of myocardial ischaemic events

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No currently available methodology exists to monitor continuously the status of regional myocardial revascularization in the postoperative patient In an effort to elucidate a metabolic indicator of ischaemia, 10 dogs were chronically implanted with a Doppler flow probe and an inflatable balloon occluder on the left anterior descending (LAD) coronary artery Myocardial pH (MpH) electrodes and ultrasonic dimension transducers were implanted in the regions supplied by the LAD and circumflex (CCX) coronary arteries A total of 50 ischaemic events were elicited in the conscious, alert animals on postoperative days 2–10 either by atrial pacing in the presence of a LAD critical stenosis

(CS) (58±5 per cent* reduction in mean LAD flow) or by total occlusion of the LAD During CS, LAD MpH fell from 7·28±0·03 to 6·8±0·1* while systolic shortening (percentage SS) diminished from 16·2±2·6 to 9±2·3* During total occlusion, LAD MpH fell to 5·9±0·13* and percentage SS was further depressed to 1·2±0·6*. Control (CCX) data were stable during all ischaemic intervals with MpH of 7·17±0·02 and percentage SS of 13·4±0·8. Stability of the pH probes was confirmed by a negligible drift between pre-implant and poststudy calibrations. MpH fell during each intervention 67±8 s after the onset of ischaemia No significant fall in MpH was observed in the absence of concurrent regional systolic dysfunction, likewise, regional systolic dysfunction was never observed in the absence of a concurrent decrease in MpH, indicating an excellent sensitivity and specificity of the methodology Continuous monitoring of MpH by percutaneously removable electrodes should enable prompt and reliable detection of myocardial ischaemic events in the postoperative cardiac surgical patient

Values are mean±s e m., *$P<0·01$ by paired *t* test

Factors influencing local recurrence after excision and radiotherapy for primary breast cancer

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Between July 1979 and December 1986, 263 patients with primary breast cancer have been treated by tumourectomy and whole breast irradiation. Double node biopsy was obtained in all patients.

Fifty-six local recurrences have occurred in the treated breast (giving an actuarial local recurrence of 23 per cent at 8 years) Eighteen of these have been massive uncontrollable local recurrence.

We have analysed a number of factors to determine which influence local recurrences. The following proved significant.

Factor	Statistical test	*P*
Patient age (<50 years)	Fisher's exact test	<0·005
Tumour size	$\chi^2=17·26$ (1 d.f.)	<0·001
Tumour histological grade	$\chi^2=3·99$ (1 d.f.)	<0·05
Lymph node positivity	$\chi^2=7·22$ (2 d.f.)	<0·05
Vascular invasion in tumour	$\chi^2=20·75$ (2 d.f.)	<0·001
Adjacent ductal carcinoma *in situ*	$\chi^2=10·51$ (4 d.f.)	<0·05

These results indicate that a careful selection policy is required On the basis of a Cox's multivariate analysis for the independence of predictive factors we have now altered our selection policy. However the powerful effect of age is problematic in view of the patients who are likely to choose breast conservation

Surgical management of coarctation of aorta with severe tubular hypoplasia of aortic arch in the neonate

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The surgical correction of severe aortic arch hypoplasia and coarctation of the aorta in the newborn child is associated with high morbidity and mortality. Many of the currently employed corrective techniques involve the sacrifice of a major great vessel or the use of a patch or conduit. This report describes a new operation performed in ten consecutive neonates and one 11-week-old infant that does not sacrifice the left carotid or subclavian artery or require the use of prosthetic materials. The technique involves left thoracotomy, resection of all coarctation and ductal tissue, extended aortotomy done on the inferior aspect of the aortic arch and proximal descending thoracic aorta, and a primary anastomosis using microvascular technique. At the time of correction the mean age of the neonates was 4·8±1·2 days Ten of the infants were term and one was premature (24 weeks gestation) The average infant weight was 2·8±0·2 kg, with the smallest weighing 1·6 kg. Associated cardiac anomalies included ventricular septal defect (6), double outlet right ventricle (1), transposition of the great arteries (2), univentricular heart (2), atrial septal defect (1). Non-cardiac anomalies included gastroschisis in one infant, and renal failure, bronchopulmonary dysplasia and intracranial haemorrhages in the one preterm infant The overall mean length of stay in the hospital for the 10 term infants was 13·8±2·3 days. The mean length of stay postoperatively was 9±2 days for the term infants. Postoperatively, 10 infants were weaned from the ventilator within 36 h. The preterm infant with severe bronchopulmonary dysplasia required continued ventilation but achieved immediate improvement in pulmonary status. There were no gradients across the anastomoses measured directly at the time of surgery. Two infants had residual 10 mmHg gradients across the aortic arch which had reduced to 0 at 1-month follow-up There were no residual gradients at follow-up ranging from 1 to 6 months with blood pressures in all four extremities measured by Dinemap. There were no complications or deaths All infants have undergone and will continue to undergo serial blood pressure measurements, echocardiography, Imatron scanning, and nuclear magnetic resonance imaging to assess growth of the anastomosis

Utilization of new linear indices of regional contractility during coronary revascularization in man

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Previous clinical intra-operative studies have assessed regional function utilizing load dependent changes in segmental shortening To obviate this limitation, we have described linear, afterload independent indices of regional contractility in the normal canine heart. The present study was performed to apply these new indices of regional contractility to the human heart Eight patients undergoing effective coronary revascularization (mean age 59 years) were instrumented with a high fidelity intracavitary micromanometer and ultrasonic crystals placed to depict a trapezoidal area in the mid-myocardium supplied by a significantly stenotic LAD coronary artery. End systolic pressure *versus* regional area (ESPRA) and regional stroke work (integrated pressure–regional area workloop) *versus* end diastolic area (RSWA) relationships were inscribed during 20–40 s preload variations by withdrawing and infusing volume via the extracorporeal perfusion circuit. Least squares regression analysis of these data defined linear correlations, the slope of each quantitating intrinsic regional contractility before and 30 min after aortic unclamping (3±0·3 grafts, 52±5 min ischaemia).

Internal mammary artery grafting to a LAD bed with normal wall motion was done in 6 of 8 patients. No patient required postoperative inotropic support.

		Slope	*r*	Heart rate
ESPRA	pre.	12·0(2·3)	0·702	77(4)
	post	3·7(0·8)*	0·882	83(3)
RSWA	pre.	102·9(10·3)	0·942	77(4)
	post	72·6(9·4)*	0·942	83(3)

Values are mean (s.e m); *$P<0·05$ by ANOVA, RSWA (mmHg × mm^2/mm^2), ESPRA (mmHg)mm^2

These data extend the applicability of linear assessment of regional function to the pre- and postischaemic human heart Despite 'optimal' cold, blood cardioplegia, these load independent parameters reveal early postischaemic depression of regional function and will allow adjudication of improvements in myoprotective strategies aimed at amelioration of this dysfunction.

Echocardiographic indices in systolic and early diastolic phases as potential markers of acute rejection in the cardiac allograft

K. Yagyu, H. Klaeger, K. Daniels, H.G. Fieguth, M. Jurmann, Th. Wahlers, J. Cremer, G. Herrman, A. Haverich and H.G. Borst, *Hannover Medical School, Hannover, FRG*

As potential markers of acute cardiac allograft rejection, left ventricular systolic function (LVEF, percentage FS and mean Vcf) and isovolumic relaxation time in left and right ventricle (IVR-LV, IVR-RV) were evaluated by serial echocardiography. A total of 95 echocardiographic examinations were performed in 55 heart transplantation recipients without tricuspidal insufficiency from 1 month to 2 years after operation. M-mode echos were recorded at 100 mm/s within 3 h of endomyocardial biopsy (BX) LVEF, percentage FS, mean Vcf, IVR-LV and IVR-RV were measured without prior knowledge of BX results, which were graded histologically.

Mild, severe and resolving acute rejections were associated with a shortening of IVR-LV (64·1 ± 13·3, 59·2 ± 12·6 and 65·3 ± 14·2 msec) compared with no or very slight rejection (85·1 ± 18·7, 86·8 ± 23·0 msec, $P < 0{\cdot}025$–$0{\cdot}05$). IVR-RV in mild rejection (45·3 ± 11·7 msec) was also shorter than no rejection (70·5 ± 24·7 msec, $P < 0{\cdot}05$) In sequential studies of 17 patients, moderate or severe rejection could be distinguished from mild or resolved rejection with 10–30 per cent decrease in IVR-LV (sensitivity 70 per cent) Rejection was not associated with significant changes in LVEF, percentage FS or mean Vcf During acute rejection, significant changes in IVR-LV and IVR-RV were detected by echocardiography. These changes may provide markers for evaluation of the degree of the acute cardiac allograft rejection.

Analysis of leucocyte activation induced by adherence to prosthetic surfaces

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Postoperative infection associated with prosthetic device implantation is a major contributor to surgical morbidity and mortality. We developed an air pouch model to characterize host cellular responses to surgical biomaterials. Discs (5 mm) of silicone elastomer (SE) or polytetrafluoroethylene (PTFE) ($n = 10$) were implanted into pouches formed by injection of filtered air into the dorsal skin of Sprague Dawley rats Animals were killed at both 2 and 7 days and the ability of the leucocytes adhering to the implants to produce H_2O_2, a measure of cellular activation, was analysed. Dichlorofluorescein diacetate (DCFH-DA) is oxidized in the presence of intracellular H_2O_2 to form the highly fluorescent compound, dichlorofluorescin (DCF) Implants were removed, incubated for 15 min with DCFH-DA, adherent cells were lysed with 0·1 per cent Triton-X® and fluorescence was measured (Ex 488/Em 525). There was a significant difference between the amount of H_2O_2 produced by the cells adhering to PTFE compared with SE adherent cells at both 2 days ($P < 0{\cdot}000001$) and 7 days ($P < 0{\cdot}00001$) The H_2O_2 produced by cells adherent to PTFE decreased by 50 per cent at 7 days when compared with 2 days, while there was no difference between 2 and 7 days for cells adherent to SE These data suggest that prosthetic biomaterials elicit different levels of cellular activation over time and that this may be related to the differential tissue damage and rates of infection seen after prosthetic implantation

Glomerular permeability to large molecules: a marker of vascular permeability?

C.P. Shearman, P. Gosling and M.H. Simms, *Selly Oak Hospital, Birmingham, UK*

Increased urinary albumin excretion in the range 10–250 mg/l (micro-albuminuria) occurs within 60 min of commencement of surgical procedures[1] and postoperative increases in vascular permeability have been observed over a similar time period[2]. Burns and trauma are associated with transient micro-albuminuria, proportional to the severity of injury and recurring with complications[3] This prompted the suggestion that micro-albuminuria reflects a generalized increase in endothelial permeability[1].

To investigate this possible relationship microvascular permeability to fluorescein-labelled dextran was assessed in the cheek pouch of 14 hamsters Simultaneously glomerular permeability was studied by identification of the pattern of urinary dextran excretion and measurement of the percentage of large molecular weight dextran (LMD) greater than 70 000.

No perceptible leakage of dextran in the pouch preparation occurred in seven controls and the mean percentage (s d.) of urinary LMD was 7·6 (3·8) per cent Seven animals undergoing laparotomy and peritoneal contamination with gastric content all showed extravasation of dextran in the pouch after 60 min and the mean percentage LMD was 22·2 (9·4) per cent ($P < 0{\cdot}005$; Wilcoxon)

This supports the hypothesis that glomerular and vascular permeability are related. Low levels of urinary proteins can be rapidly determined and may provide prognostic information in surgical conditions.

1. Gosling P, Shearman CP, Gwynn BR, Simms MH, Bainbridge ET. Microproteinuria response to operation. *Br Med J* 1988, **296**: 338–9
2. Gosling P, Sutcliffe AJ, Cooper MACS, Jones AF. Burn and trauma associated proteinuria: the role of lipid peroxidation, renin and myoglobin. *Ann Clin Biochem* 1988; **25**: 53–9.
3. Fleck A, Raines G, Hawker F *et al* Increased vascular permeability. a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985; **i**. 781–4.

Effects of vitamin A on endotoxin and complement function in peritonitis in the rat

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Demetriou[1] had previously shown a significant increase in rat survival after experimental peritonitis when the rats were treated with vitamin A before the operation The aim of this study was to try to find a more objective cause for the difference in survival time.

We investigated whether vitamin A had any effect on the endotoxin and complement production in the peritonitic rat. The rats were fed with a vitamin A-free diet for 6 days. One group received vitamin A intramuscularly (six times the recommended intake· 6×230 IE kg^{-1} day^{-1}) and one group was given the vehicle (peanut oil) only. The rats were then operated on and peritonitis was initiated by caecal perforation. Blood samples were taken at intervals to follow the concentration of endotoxin and complement.

The group that received vitamin A injections showed markedly lower endotoxin levels than untreated animals ($P < 0{\cdot}01$) There was a marked difference in the concentration of complement factors (C3, C4) between treated and untreated animals ($P < 0{\cdot}01$)

These results indicate that vitamin A has a positive effect in postoperative peritonitis, when given pre-operatively.

1. Demetriou AA. *Arch Surg* 1984; **119**: 161–5.

Tumour necrosis factor is an effective immunomodulator of surgically simulated wound infection in mice

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Tumour necrosis factor α (TNF) has several immunoregulatory properties, and has recently been shown to be effective pretreatment but not therapy in a limited number of microbial infections. This study assessed the efficacy of TNF as prophylaxis and therapy in a murine model of surgically simulated wound infection. Bacterial challenge consisted of a *Klebsiella pneumoniae*-laden suture inserted into the mouse thigh, combining the elements of pathogenic bacteria, tissue injury and a foreign body. Groups of CBA/J mice received either TNF or control injections subcutaneously TNF was administered daily at a dose of 7500 units. Mice pretreated for 5 days before suture challenge survived significantly longer than controls Systemic bacterial recovery was significantly reduced in the TNF pretreated group on days 1, 2 and 3 after suture challenge, and local bacterial recovery was significantly ($P < 0{\cdot}05$) reduced on day 3 after suture challenge When therapy was commenced 1 h after suture challenge and continued for 7 days, 12 of 20 mice survived, significantly greater than 4 of 20 surviving controls. These data confirm that TNF is effective in pretreatment of *Klebsiella pneumoniae* infection in mice. Furthermore, this is one of the first reports of therapeutic efficacy commencing after bacterial challenge of TNF in treatment of a bacterial infection.

Perforation of the inflamed appendix during clinical observation: a prediction

J.R. Clarke and F.T. deDombal, *Medical College of Pennsylvania, Philadelphia, USA, and University of Leeds, Leeds, UK*

It is not possible to measure directly the rate at which the inflamed human appendix perforates during clinical observation. A method of estimating the probability of perforation for any observation period is proposed. It is based on the hypothesis, never validated, that the probability of perforation is a logistic regression function of the duration of pain and the age of the patient[1]. If true, the probability of perforation during an observation period is then a function of the patient's age, the duration of pain on presentation, and the length of observation[2]. To test these hypotheses, predicted perforation rates were compared with actual perforations for 690 patients with durations of pain from 3 h to 8 days and ages from 2 to 83 years in five hospitals on four continents. The method predicted 206 perforations, which were consistent with the 200 perforations observed, as tested by the χ^2 test of goodness of fit (*Table 1*). Predicted perforations were consistent with those observed for cohorts with durations of pain of <24 h, 24 h and 48 h by the same goodness-of-fit test.

Table 1 *Predictions of perforated appendices*

Interval	0	10	20	30	40	50	60	70	80	90	100%
Predicted		11	13	23	31	21	15	15	19	17	41 patients
Observed		12	19	22	29	20	17	13	18	13	37 patients
n		219	96	96	90	49	28	24	25	20	43 patients

$\chi^2 = 5·09$, d.f. $= 9$, P(Ho) 0·80

The proposed method for calculating the probability of perforation for any observation period appears justified and should produce clinically informative predictions (*Table 2*).

Table 2 *Perforation rates during an 8-h interval*

	Age				
Duration of pain	5 years	10 years	20 years	40 years	60 years
12 h	25	7	4	10	37
24 h	23	9	5	11	30
36 h	19	9	5	11	22

Values are percentages

1. Koepsell TD, Inui TS, Farewell VT. Factors affecting perforation in acute appendicitis. *Surg Gynaecol Obstet* 1981, **153**: 508–10
2. Clarke JR. A concise model for the management of possible appendicitis. *Med Decis Making* 1984, **4**: 331–8.

Effect of endotoxin on antigen presentation after caecal ligation and puncture

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The effect of endotoxin (LPS) on macrophage (ϕ) antigen presentation (AP) following sepsis is unclear. After caecal ligation and puncture (CLP), a statistically higher mortality has been noted in LPS-sensitive C_3H/Hen mice (HEN) compared with C_3H/Hej mice (HEJ) that are LPS-resistant[1]. The current study was designed to examine the effect of LPS on ϕ AP to T cells after CLP in HEN and HEJ.

HEJ and HEN mice ($n = 20$ per group) underwent CLP with a 25 gauge needle, and were killed by cervical dislocation on days 1, 7 and 14. Splenic ϕ were obtained for culture from experimental animals and syngeneic controls. These ϕ were co-cultured with T helper cell clone, D10 G4.1, in the presence of its specific antigen (conalbumin); ϕ AP was measured by D10 G4.1 proliferation[2].

Mortality from CLP by day 14 was 45 per cent for HEN and 0 per cent for HEJ ($P < 0·05$, χ^2). Data for ϕ AP of HEN and HEJ after CLP were expressed as a percentage of control ϕ AP, and statistical differences were analysed using the Mann–Whitney *U* test. On day 1 after CLP, ϕ AP was normal for both HEN (89 per cent) and HEJ (102 per cent). On day 7, however, ϕ AP was significantly decreased for HEN (60 per cent, $P < 0·05$) and significantly decreased for HEJ (141 per cent, $P < 0·05$). On day 14 after CLP, ϕ AP returned to normal for both strains. Interleukin 1 (IL-1) levels of HEN mice were elevated after CLP—highest on day 7 (260 per cent) and lowest on day 14 (110 per cent).

HEN mice had increased mortality after CLP (*versus* HEJ), associated with a significant depression of ϕ AP on day 7 after CLP. This defect in ϕ AP in these LPS-sensitive mice did not appear to be due to inadequate ϕ production of IL-1 by HEN. The LPS-resistant HEJ mice all survived after CLP, and had normal or enhanced ϕ AP. Since HEN and HEJ differ only in their responsiveness to LPS, these data suggest that endotoxin has an important effect on ϕ–T cell interactions in antigen presentation.

1. Baker CC, Kupper TS. Clarification of the role of endotoxin in intra-abdominal and systemic sepsis. *Surg Forum* 1985, **36**: 68–70
2. Kaye J, Gillis S, Mizel SB *et al.* Growth of a cloned helper T cell line induced by a monoclonal antibody specific for the antigen receptor. *J Immunol* 1984; **133**: 1339

Is gluconeogenesis following endotoxaemia mediated by stress hormones?

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Accelerated gluconeogenesis and hyperglycaemia are characteristic metabolic changes following critical illness. To test the hypothesis that these alterations are caused by elevated concentrations of stress hormones, we determined the rate of glucose production in healthy volunteers ($n = 6$) receiving bolus intravenous *E. coli* endotoxin (4 ng kg^{-1}) or saline in paired studies. Further subjects ($n = 6$) were pretreated with the cyclo-oxygenase inhibitor ibuprofen (1600 mg orally) before endotoxin or saline. Subjects received a bolus injection (2·4 mg kg^{-1}) followed by a continuous infusion (0·03 mg kg^{-1} min^{-1}) of the tracer isotope 6-6,D_2-glucose, and glucose production rate (Ra glucose) was determined 4 h after endotoxin/saline injection using the Steele equation. Serial measurements were made of circulating concentrations of glucose and pituitary and stress hormones. A portion of the data is shown, given as mean ± s.e.m.

	Ra glucose (mg kg^{-1} min^{-1})	Glucose (4 h) (mg dl^{-1})	Peak cortisol (μg dl^{-1})	Peak epinephrine (pg ml^{-1})	Peak glucagon (pg ml^{-1})
Saline	2·0 ± 0·0*	85 ± 2	12 ± 2	60 ± 1	113 ± 22
Endotoxin	2·6 ± 0·1	95 ± 4*	32 ± 2*	150 ± 34*	213 ± 57
Saline/ ibuprofen	2·8 ± 0·1	83 ± 2	10 ± 1	47 ± 10	172 ± 13
Endotoxin/ ibuprofen	3·8 ± 0·4	77 ± 7	17 ± 1	78 ± 14	187 ± 22

* Different to the other three groups, $P < 0·05$ by ANOVA (Dunnett *t* test)

Plasma insulin concentrations were similar in all groups. Ra glucose was increased by 30 per cent after endotoxin administration but was also increased by ibuprofen alone. Despite attenuation of stress hormones in the endotoxin/ibuprofen group increased gluconeogenesis still occurred. These data suggest that endotoxin, associated cytokines or other factors also mediate accelerated glucose production in sepsis and injury.

Fine needle aspiration biopsy (FNAB) provides early rejection diagnosis in canine pancreatic transplantation

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As an independent marker of rejection in pancreatic transplantation with bladder exocrine drainage, falling urinary amylase (UA) precedes hyperglycaemia, but often occurs too late to permit reversal. In this longitudinal study, FNAB was correlated with UA and graft histology. Sixteen dogs received total pancreatic allografts, ten without immunosuppression and six with triple therapy. FNAB and core biopsies were performed thrice weekly or at any point due to disease or rejection (UA <5000 units/l). Aspirate material was evaluated as increments of inflammatory cells corrected for blood counts. Total corrected increment (TCI) increased significantly from 1·0±0·4 (mean±s.e.m.) to 3·0±1·2 between 6 and 4 days before functional rejection, owing to infiltration of blast cells and macrophages ($P<0{\cdot}05$) TCI of healthy immunosuppressed grafts was below 1·6 up to 30 days after transplantation but was greater than 5 with pancreatitis or rejection. Histological diagnosis of minimal change had significantly lower TCI than acute rejection ($P<0{\cdot}003$) and pancreatitis ($P<0{\cdot}001$). Rejection and pancreatitis were distinguished by significant differences of monocyte and macrophage increments. Low UA levels were a marker of end-stage rejection only In contrast, FNAB assessment provided an early and potentially treatable diagnosis of acute rejection

Reticuloendothelial system (RES) function in surgical patients: the role of opsonins

M.C. Aldridge, S. Cheslyn-Curtis, J.E J. Biglin, J. Dye, B. Pratt*, S.J.D. Chadwick, H.A F. Dudley, *St. Mary's Hospital, London W2, UK*

Opsonic depletion may occur in patients following surgery[1] and it has been suggested that this results in depression of RES function[2] There have, however, been no clinical studies which have attempted to correlate opsonin levels with RES function measured independently. We have previously reported the use of the clearance kinetics of technetium tin colloid (TTC) in the detection of RES depression following surgery and during sepsis in the rabbit[3] and suggested that it may be suitable for use in man.

Kupffer cell extraction of TTC was measured in pre-operative (Group A, $n=20$) and postoperative patients (11 uncomplicated (Group B), and in 9 critically ill patients with abdominal sepsis (Group C)) The opsonic proteins C_3, IgG and fibronectin were measured in patients pre-operatively and sequentially throughout the postoperative period

	Pre-operative ($n=20$)	Postoperative ($n=11$)	Critically ill ($n=9$)
$t_{\frac{1}{2}}$ TTC (min)	1·47±0·08	2·22±0·21*	2·46±0·18**
Liver spleen ratio (TTC uptake)	2·77±0·40	1·96±0·33†	—

		Days 1–3	Days 4–6	Days 7–8	
C_3 (percentage of control)	128±6	94±4**	114±4	121±7	72±3*
IgG (mg/ml)	10·6±1·5	7·2±0·7†	7·2±0·7†	8·0±0·6	8·0±0·8
Fibronectin (percentage of control)	100±5	68±4**	88±5	111±17	50±8**

Values are mean±s.e.m. $^{*}P<0{\cdot}01$, $^{**}P<0{\cdot}001$; $^{\dagger}P<0{\cdot}05$, Mann–Whitney *U* test

There was a significant negative correlation between the level of plasma fibronectin and postoperative RE function (TTC clearance) in both uncomplicated and critically ill patients ($r_s=-0{\cdot}7$, $P<0{\cdot}001$ Spearman's rank correlation coefficient) but no correlation between RE function and levels of either C_3 or IgG These results suggest that reduction in levels of fibronectin may be an important factor in RES depression in patients following uncomplicated major surgery and during sepsis and support the concept of immunomodulation by fibronectin replacement.

1. Gauperaa T, Giercksky K-E, Pevhaug A, Rekvig OP. Fibronectin, complement and immunoglobulins in serum after surgery. *Br J Surg* 1985; **72**: 59–62.
2 Saba TM, Blumenstock FA, Shah D *et al* Reversal of fibronectin and opsonic deficiency in patients. A controlled study *Ann Surg* 1984, **199**: 87–96.
3. Aldridge MC, Chadwick SJD, Biglin JEJ, Dudley HAF. Reticuloendothelial failure during severe sepsis—an intrinsic Kupffer cell defect? *Br J Surg* 1986; **73**· 498

Surgical Research Society

The 69th meeting of the Surgical Research Society will take place at the University of Kent, Canterbury, Kent, UK, on 5 and 6 January 1989. For information contact Hilary Thompson, The London Hospital, London E1 1BB, UK

Correspondence

Does breast cyst type predict for breast cancer risk? A question still to answer

Sir

I was disappointed to read the recent paper of Messrs Ebbs and Bates (*Br J Surg* 1988, **75**: 702–4) as their data failed to justify either of the claims made in the title.

Despite the 4-year period they have taken to recruit their patients they present a median follow-up time of 5 months implying a substantial proportion of their patients had been followed up for nearer the minimum 3 months.

Their statistical analysis is flawed as they take no account of time to recurrence of their cysts. The analysis should have been carried out using the Kaplan–Meier log rank test, or else a fixed time at which patients were designated as recurrent or non-recurrent cyst formers should have been used to compare the groups. For example, if all 14 women with flattened cysts recurred after more than 2 years follow-up whilst all 16 women with apocrine cysts recurred at 6 months, their data would tend to confirm those of Dixon[1] which they seek to disprove.

Most studies of electrolyte analysis[1,2] have found that 75 per cent of women produced apocrine cysts, yet Ebbs and Bates claim only 50 per cent of their women were apocrine cyst formers and do not comment on this surprising finding. Doglotti[2] and the Edinburgh Group[1] have independently found a 70 per cent concurrence of electrolyte type amongst multiple synchronous breast cysts and Ebbs and Bates' data of 62 per cent concurrence may have substantiated the other papers if the remaining 14 per cent of cysts had undergone electrolyte analysis.

In my experience of 122 women in two centres who have had breast cysts aspirated and are followed up for 6 months or longer, 2 out of 38 women with flattened cysts and 29 out of 83 women with apocrine cysts have developed further cysts within 6 months of their initial cyst aspiration ($P<0.002$, χ^2 test with Yates' correction). Sequential cysts have remained a stable type in 90 per cent of cases.

Finally, by definition Haagensen's original[3] and all subsequent studies of the risk of breast cancer development after cyst aspiration have excluded any cyst aspirated within a year of cancer being diagnosed and all cysts aspirated after breast cancer development. This would exclude all the patients presented in Ebbs and Bates' paper.

Thus this paper does not prove breast cancer risk is not related to cyst type and has such inadequate follow-up data that few conclusions can be made regarding the natural history of cystic disease.

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1. Dixon JM, Scott WN, Miller WR. Natural history of cyst disease: importance of cyst type. *Br J Surg* 1985, **72**: 190–2.
2. Doglotti L, Orlandi F, Torta M *et al*. Cations and dehydroepiandrosterone-sulphate in cyst fluid of pre and post menopausal patients with gross cystic disease of the breast. Evidence for the existence of subpopulations of cysts. *Eur J Cancer Clin Oncol* 1986, **22**: 1301–7.
3. Haagensen CD. *Diseases of the breast*. 3rd ed. Philadelphia: W.B. Saunders, 1986: 250–66.

Letter 2

Sir

Whilst the title of the recent paper by Ebbs and Bates (Breast cyst type does not predict the natural history of cyst disease or breast cancer risk. *Br J Surg* 1988; **75**: 702–4) accurately reflects the statement in their summary that 'cyst type was not predictive of further cyst development, neither was a particular cyst type associated with the development of, or a history of, breast cancer', their data can hardly support the conclusions, for the following reasons.

1. The median length of follow-up for cyst recurrence of 5 months is insufficient to make definitive statements on the natural history of cystic disease which may stretch over a decade of years.

2. The thesis that apocrine hyperplasia associated with cysts is a risk factor for breast cancer is largely based on subsequent development of cancer[1]. Only two cases from the Ebbs and Bates paper fall into this category, diagnosed 9 and 10 months after cyst aspiration. Even allowing for the small numbers, the length of follow up is totally inadequate[2]. Given the age distribution of cysts and cancer, to resolve this issue it will take 10–20 years of follow-up of patients with breast cysts. In this respect a conference is being organized in the USA later this year to address this specific question and I know that groups in the USA, Italy, Wales and ourselves have data on larger numbers of patients with longer follow-up, but even so we consider the results too premature to justify publication.

3. Data on a previous history of breast cancer is again based on two cases.

4. The remaining cases are women in whom cysts were aspirated from the area of a co-existing carcinoma. Caution needs to be exerted in extrapolating these results. It is our experience that many such fluids probably do not represent true cysts but rather some form of tumour exudate. For example these fluids usually do not have the classical pattern of proteins[3] associated with breast cyst fluids.

The authors misinterpret papers from Dogliotti[4] and ourselves[5] which indicate the tendency for multiple cysts to be of the same type—not an absolute consistency. Indeed a similar trend is obvious in the data of Ebbs and Bates.

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1. Haagensen CD. Cumulative predisposition to carcinoma of the breast. In: Haagensen CD, Bodian C, Haagensen DE, eds. *Breast Carcinoma: Risk and Detection*. London: Saunders, 1981: 366–8.
2. Haagensen CD. Gross cystic disease of the breast. In: Haagensen CD, Bodian C, Haagensen DE, eds. *Breast Carcinoma: Risk and Detection*. London: Saunders, 1981: 72–5.
3. Haagensen DE *et al*. Breast gross cystic disease fluid analysis. I. Isolation and radioimmunoassay for a major component protein. *J Natl Cancer Inst* 1979, **62**: 239.
4. Dogliotti L, Orlandi F, Torta M *et al*. Cations and dehydroepiandrosterone-sulfate in cyst fluid of pre- and menopausal patients with gross cystic disease of the breast. Evidence for the existence of subpopulation of cysts. *Eur J Cancer Clin Oncol* 1986; **22**: 1301–7.
5. Dixon JM, Scott WN, Miller WR. Natural history of cyst disease: importance of cyst type. *Br J Surg* 1985; **72**: 190–2.

Authors' reply

Sir

We welcome the opportunity to reply to the comments made by Miller on the hypothesis that a low sodium to potassium ratio in (apocrine) breast cysts predicts the development of multiple cysts and breast cancer.

We reported a pragmatic attempt to determine the value of the measurement of breast cyst electrolyte concentration. In our study the frequency and need for follow-up was based on clinical judgement. It seems inappropriate to follow these patients for decades when a median follow-up of 5 months indicates that the proposed predictor failed to remain constant for an individual. To redemonstrate the variability of cyst cation ratios in cysts from individual patients, we have plotted the cation ratio from the first cyst aspirated from a patient against the ratio of the first recurrent cyst for the 25 patients for whom data are available (*Figure 1*). Stability of cyst cation ratio would be indicated by a correlation coefficient of 1.0. The correlation coefficient from our data is actually 0.008: there is no correlation.

We reported data on 101 consecutive new patients with breast cysts including eight women with a history of, or the subsequent development of, breast cancer. Accepting Dupont and Page's findings[1] that overall breast cysts do not carry an increased risk of breast cancer we would expect one in, say, 14 women to develop cancer in this cohort, i.e. approximately 7. Since the first analysis of our data another woman has subsequently developed Stage I breast cancer approximately 2 years after two cysts were aspirated from the same breast. One cyst was apocrine in type (sodium:potassium ratio = 0.25), the other cyst was flattened (sodium:potassium ratio = 14.24). Obviously cyst type was not a predictor for this individual. We did not report this case in our paper because it occurred after the analysis of our data and would have constituted selection bias. We have therefore observed 9 tumours in 101 women and perhaps learnt more about the non-association of cyst type and breast cancer than we might have hoped from this cohort. We would argue therefore that presentation of our results is not premature. We feel in fact that it is important that we publish our negative results in view of the multiplicity of positive results published on this subject from Miller *et al*. before the hypothesis becomes established as dogma.

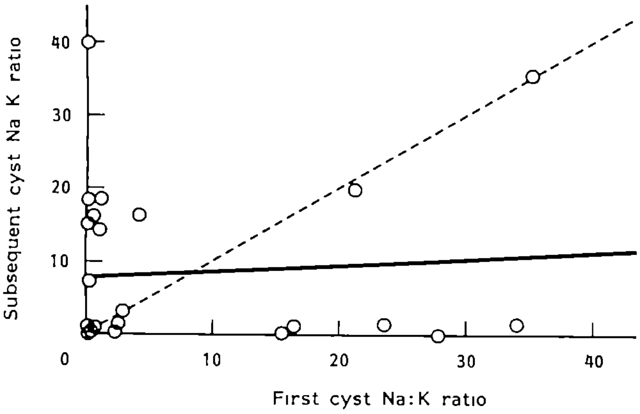

Figure 1 ---, *Theoretical regression line* (r = +1·0), ——, *calculated regression line* (r = 0·008)

We are intrigued by the concept of localized oedematous collections clinically mimicking cysts related to breast tumours

We agree that there is a tendency in patients who have multiple cysts for the cysts to be mainly apocrine This is only a tendency and, as Miller agrees, is not absolute. The trend appears stronger in the Scottish data and may in fact only be a sampling bias if our hypothesis that cysts all develop as apocrine and then mature to flattened is true. Previous studies, including those from his unit, have not indicated their frequency of follow-up: we suspect patients were seen at short intervals. In this setting a high proportion of immature apocrine cysts would have been detected With time some of these cysts may not have been detected clinically as they dispersed or would change type as they matured to become flattened cysts Follow-up protocols may introduce selection bias and might explain the large difference in magnitude seen between the two centres.

The study of the evaluation of risk factors for the subsequent development of breast cancer is largely one of failures of proposed predictors. Whatever his prejudices, Mr Miller must accept that our results show that breast cyst type is not constant for an individual, it does not predict whether further cysts will develop or what type they will be. Its inconsistency means that it does not, and cannot, predict the risk of a subsequent breast cancer[1].

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T. Bates

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1 Dupont WD, Page DL Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; **312**: 146–51.

Doppler ultrasonography in the diagnosis of acute scrotal pain

Sir

I wish to add a note of caution on the use of Doppler ultrasonography in diagnosing testicular torsion (*Br J Surg* 1988, **75**· 238–9). I have been using the Doppler ultrasound in the manner recommended by Bickerstaff and his colleagues and have had two false negatives with this technique. These were both in 15-year-olds with intravaginal torsion where on pointing the Doppler to the lower pole of the testis, there appeared to be no reduction in flow compared with the other side Both torsions involved the cord close to the testis and in one patient the blood supply to the distal half only was impaired These patients support their view that a careful clinical assessment is necessary for safe interpretation of Doppler results.

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Colonic haemorrhage

Sir

We have read with interest the view of Berry *et al.* (*Br J Surg* 1988, **75**: 637–9) on the management of colonic haemorrhage.

We wholeheartedly support their concept that a thorough search be made to identify the source of bleeding and decry blind colonic resection.

The need to exclude upper gastrointestinal bleeding is important, though surely they cannot seriously advise that nasogastric aspiration be used as a method of exclusion Brisk duodenal bleeding can present with fresh blood per rectum and gastroduodenoscopy should be mandatory before any other more invasive procedure.

In our view it is ill advised to rule out preoperative arteriography which may be helpful and is readily available at most district general hospitals. Selective arteriography has the advantage of looking at the coeliac axis, superior and inferior mesenteric vessels. If a bleeding point is confirmed the catheter may be left *in situ* to help in the identification of the bleeding point This is particularly useful in bleeding from the small bowel.

If arteriography is not helpful we would agree with the approach of laparotomy, antegrade washout and colonoscopy. A technical point is that colonic mobilization be avoided before colonoscopy or the appearances of angiodysplasia may be masked by mural bruising. Should colonoscopy be unhelpful, endoscopy of the small bowel should be performed

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Authors' reply

Sir

In reply to the letter from Messrs N Karanjia, D Schache and M Rees, we accept that the most reliable way of excluding gastroduodenal bleeding is by oesophagogastroduodenoscopy. However, if the nasogastric aspirate contains obvious bile with no trace of blood in a patient with brisk gastrointestinal bleeding, we feel that it is unlikely that bleeding will be from that area.

With regard to their comments on pre-operative angiography, we have shown that this investigation in patients with major colonic haemorrhage is both hazardous and unhelpful[1]. Patients with continuing major bleeding require emergency surgery and on-table colonoscopy with antegrade irrigation to identify the source of bleeding This technique is simple, requires no specialized expertise and is within the capabilities of any general surgeon. An experienced colonoscopist is not essential as the instrument can be easily guided round the colon by the assistant.

Even if a radiologist with the necessary experience of emergency selective mesenteric angiography is 'readily' available (as the correspondents claim) the technique confers no advantages and delays potentially life saving surgery. We feel that time should not be wasted on pre-operative angiography in these patients

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M. G. W. Kettlewell

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1. Cussons PD, Fletcher EWL, Berry AR. A comparison of value of mesenteric angiography and on-table colonoscopy in massive acute large bowel haemorrhage. *Gut* 1988, **29**. A727.

Use of drains after cholecystectomy

Sir

We were interested to read the article by Irwin *et al* (*Br J Surg* 1988, **75**: 476) indicating that drains may be unnecessary after cholecystectomy. In February 1987 we decided to abandon the routine use of drains after cholecystectomy having previously always inserted a number 10 Fr Exudrain (Astra Meditec): this drain had usually resulted in the collection of about 50 ml of fluid. We have studied the effect of this policy change by comparing the results in the 54 patients operated on before and the 87 patients after the change.

A standard cholecystectomy technique was being used throughout. In the first group, drainage was not used in two patients and in the second group it was deemed prudent to insert drains on two occasions.

These four patients were included in the analysis. The 54 patients in the 'drain' group had a median age of 56·5 years (range 19–76) and the 87 in the 'no drain' group had a median age of 52 years (range 16–84). This difference was significant ($U = 1746$, $P = 0·04$). All elective, urgent and emergency operations were included.

One patient died as a consequence of pre-existing disease.

The postoperative hospital stay actually fell from a median of 5 days (range 3–12) to 4 days (range 2–45) ($U = 1601$, $P = 0·02$).

When drainage was used there were complications in six cases (jaundice due to Omnopon® (Roche Products Ltd., UK) infusion (1), cellulitis (1), bile leak after common bile duct puncture cholangiogram (1), urinary infection (2) and chest infection (1)).

In the cholecystectomies without drainage, there were 5 complications (unexplained hypotensive episode (1), wound bruising associated with heparin use (1), urinary retention (2) and pyrexia of unknown origin (1)). In particular we have not seen any subhepatic or subphrenic collections although routine scanning has not been used.

Our results clearly show that routine drainage after cholecystectomy is unnecessary and may possibly contribute to a longer hospital stay.

J. Beynon
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Operative treatment of median cervical cysts

Sir

We read with interest the paper by Tetteroo *et al* (*Br J Surg* 1988; **75**: 382–3) which re-emphasizes the importance of removing the central portion of the hyoid bone in the surgical management of thyroglossal duct remnants.

Our own experience of 35 patients operated on for this pathology during the period 1983–87 is very similar. There were 18 women and 17 men with an age range of 1–71 years. All these patients had a history of a lump at or close to the midline of the neck, but the duration of symptoms ranged from only a few days to 20 years. We had eight cases of recurrent disease (23 per cent). Six of these patients had neither excision of the body of the hyoid bone nor tongue base dissection at the primary operation and, although in the other two the hyoid had been removed, no dissection of the thyroglossal tract to the foramen caecum had been attempted.

In his classical paper in 1920, Sistrunk suggested that surgical treatment of thyroglossal duct remnants should include excision of the body of the hyoid bone and the soft tissues extending to the foramen caecum[1]. This method was based on sound embryological principle as the thyroglossal tract passes through the centre of the second branchial arch which elaborates the hyoid bone. Seventy years later recurrent disease is still encountered when this simple principle is ignored by leaving the hyoid bone *in situ*.

M. L. Nicholson
J. F. Sharp
J. P. Diver

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1 Sistrunk WE. The surgical treatment of cysts of the thyroglossal tract. *Ann Surg* 1920, **71**: 121–4

Treatment of gastric varices

Sir

The paper by Sarin and his colleagues (*Br J Surg* 1988 **75**, 747–50) advocates prophylactic injection of gastric varices. Their own results fail to justify such a policy.

Of their 309 patients undergoing sclerotherapy for varices, only 48 had gastric varices. In eight, gastric varices were considered to be the source of bleeding but in only five was bleeding observed and for at least two of these the cause was iatrogenic ulceration from previous injections. Thus, there was proven spontaneous gastric variceal bleeding in about 1 per cent of their patients.

They then took 32 patients who had never bled from gastric varices and entered them on a programme of injection sclerotherapy. Only 12 achieved obliteration and 11 died in the attempt. Eight of these deaths were due to uncontrolled bleeding from gastric varices which had never previously bled. This gives a mortality of 34 per cent for prophylactic injections compared to only 25 per cent in their eight patients who were actively bleeding from gastric varices.

Gastric varices, unlike oesophageal varices, are protected by the muscularis mucosa and to damage this layer and the overlying mucosa by injection sclerotherapy is foolhardy. Since gastric varices rarely bleed spontaneously, I counsel a policy of masterly inactivity for non-bleeding gastric varices.

G. W. Johnston

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Wound healing properties of honey

Sir

How delighted I am to read the paper by Mr S. E. E. Efem (*Br J Surg* 1988, **75**: 679–81) concerning the wound healing properties of honey. I can only concur with his findings and I have been using this material myself for a number of years to clean up infected wounds, particularly around the face following trauma. Its use does seem to provoke hilarity amongst one's colleagues until they have tried it. Apart from its efficacy I find it is particularly useful in that it is so easily removed by simple bathing, being of course water soluble, compared with many other preparations which are in a greasy base.

As regards its method of action, I agree with Mr Efem that hypertonicity is likely to be the answer and it has certainly served the fruit preserving industry well for many years! In this part of the country where honey seems to be a luxury, I can assure you that golden syrup seems to work just as well.

A. E. Green

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Sigmoidoscopy in the Indian bowel

Sir,

We read with interest the article by Mann *et al* (*Br J Surg* 1988, **75**: 425–7) on factors which determine a successful sigmoidoscopy. We were surprised by the high frequency of unsatisfactory procedures that they encountered in patients not previously prepared. That this is not a universal experience can be appreciated from our data.

We analysed retrospectively the records of the last 124 patients (84 males, 40 females, aged 10–77 years, mean 38 years) on whom we undertook the procedure on an outpatient basis. The procedure is usually performed between 09.00 hours and 11.00 hours, which is roughly about 2–4 h after the average Indian relieves himself. No preparatory diet or medication is advised. We use the knee–elbow position routinely since previous experience showed us that it was more convenient to the operator and so to the patient.

The bowel preparation was reported as fair (17 cases) or good (89) on a poor–fair–good scale in 85·5 per cent of cases. The 'scope could be passed to a distance of more than 20 cm in 84·5 per cent (we excluded from analysis those in whom the procedure was abandoned earlier for reasons other than bowel preparation). We agree with the contention that it makes no difference who performs the procedure as long as a few months' background training is available.

Obviously, it matters not who does it, but on whom. The Indian bowel comes prepared for the occasion.

P. Abraham
S. J. Bhatia
D. H. Pipalia

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India

Book reviews

The Medical Management of Breast Cancer

C J. Williams and R B. Buchanan 246 × 189 mm Pp 340 1987 Tunbridge Wells Castle House Publications £45 00.

The whole spectrum of the management of breast cancer from epidemiology to screening to diagnosis and treatment is covered by this text. It is in large parts excellent.

The authors state that multi-author texts have the disadvantage of giving neither a balanced nor a unified view The advantage of a multi-author text, however, is that each section is written by an expert in that field and who is more likely to have a full knowledge of all the relevant literature. Two authors cannot know about all aspects of the treatment of breast cancer and this is reflected in some parts of the text which fail to give the balanced and unified view that the authors wished to achieve. This is particularly apparent in the discussion of the relationship of benign breast disease and breast cancer. Major references have been omitted They leave the reader with the view that large numbers of women with benign disease are at increased risk of breast cancer This is now known not to be the case Other omissions are the absence of the Peto overview when dealing with adjuvant oöphorectomy There are also a number of errors in the text and references. The errors include three in a single table. These problems can, however, be sorted in the next edition

Apart from these problems, the authors have provided a comprehensive and well referenced overview of the management of breast cancer and I think it is a useful addition to the literature. I found it very useful for preparing talks and it is a book that can be recommended to all associated with patients with breast cancer.

J. M. Dixon

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Cranio-Facial Deformities

D J Dacid. 170 × 242 mm Pp. 138 Illustrated 1987. North Adelaide Australian Cranio-Maxillo-Facial Foundation. 20 $A

Writing a simple guide to an extremely complex subject presents, in many ways, a greater challenge than the preparation of a specialist text. The aim of this little book from the South Australian Cranio-Maxillo-Facial Foundation is to summarize the scope of craniofacial surgery for non-specialist, medical and paramedical personnel as well as patients and their families The presentation, by the University of Adelaide, is simple with many black-and-white photographs to illustrate each written page. In general these are of adequate quality. The book is divided into five sections. The first introduces the reader to the aetiology, genetic basis and progress of craniofacial deformities Part two, which constitutes two-thirds of the book, contains seven chapters covering abnormal head shapes, major syndromes, facial asymmetry, clefts, mouth and jaw problems, abnormal masses and injuries Each is brief and descriptive detailing the major features of the abnormality with its functional and psychological implications. The balance between providing an excess of confusing data and leaving the reader without a clear picture of a problem is fine, but in general the authors have achieved it. Details of genetic inheritance patterns and risks are particularly helpful The intricacies of Tessier's classification of facial clefting patterns could have been abbreviated and the section on gunshot injuries omitted altogether. Parts three and four, covering diagnosis and management, detail the make-up of a craniofacial team and the roles of its members, a description of some specialized investigations such as computerized tomography and a very brief insight into the surgical possibilities The importance of treating these conditions under the umbrella of a formally constituted unit is apparent. Space is given to possible complications of surgery and the operations are placed in a very realistic context Finally the influence of growth on both deformity and its surgical correction is stressed. The need for long-term follow-up care and secondary surgical procedures is demonstrated If one were to level criticism it would be that the authors have tried to cover too much Perhaps a better result would have been achieved with a more generalized overview, concentrating on the major syndromes and omitting cleft lip and palate. The latter is covered only very briefly and without any indication of what may be expected following treatment The book would be useful in medical school and paediatric unit libraries but of limited value to a layman or parent.

B. Jones

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Liver Transplantation. Second edition

R. Calne. 157 × 232 mm. Pp. 539 Illustrated 1987 Philadelphia· W B. Saunders $69 50.

The number of patients undergoing liver transplantation has grown rapidly during the last 4 years. The increasing success of the operation followed the improvement in survival reported by Starzl after the introduction of cyclosporin and the favourable report of the NIH Consensus Development Conference in 1984 This book is based on the second largest series of liver transplants performed by the Cambridge–King's College Hospital teams and the data from more than 350 cases provide a valuable record of the evolution of treatment from the early 'experimental' days of 1968 until 1985 when more than 60 per cent of patients survived more than 1 year after their transplant operations

The first edition of this book contains an analysis of 120 operations performed over 14 years and it is a measure of the increased importance of the transplant programme that the second edition reports a similar number performed over 4 years Early deaths within 14 days of operation are now unusual and have fallen by more than 50 per cent Chronic rejection unresponsive to medication is now believed to be the major cause of late graft failure in long-term survivors. It was recognized in 11 per cent of 227 cases and a second transplant is probably required for the treatment of this problem.

Other causes of graft failure included haemorrhage and thrombosis of the hepatic artery or portal vein. Hepatic artery thrombosis was a particular problem in the paediatric age group and it is of interest that 3 out of 13 patients with Budd–Chiari syndrome suffered a repeat thrombosis of major veins The biliary tract continues to pose problems in transplant surgery, these problems include bile leaks, early and late stricture formation and the formation of biliary concretions

The most common outcome of transplantation for hepatic tumours was recurrence and, although this was the most common reason for operation in the first half of the series (45 per cent of cases), only three patients were alive at the time of publication

The book comprises all aspects of the management of a patient undergoing liver transplantation and 46 contributors are responsible for topics which include experimental techniques, patient assessment, operative treatment, pathological data and the results of surgery It is a full record of an important endeavour in British surgery and it is a pity that it is sometimes spoiled by spelling errors and poorly reproduced photographs, some of which are unnecessary The discussions on liver resections for the provision of hepatic segments for paediatric patients and the costing of transplant procedures in the UK are only considered briefly and should be amplified in any future edition.

This book contains a wealth of information and should be read by any surgeon interested in the development of liver surgery and transplantation techniques

E. R. Howard

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Basic Microsurgical Techniques

C Green. 210 × 295 mm. Pp 39 Illustrated Middlesex MRC Clinical Research Centre. £7 00

This laboratory manual on *Basic Microsurgical Techniques* is warmly recommended to all surgeons potentially interested in this taxing field. The manual is beautifully laid out, concise and comprehensive and has a useful appendix detailing further reading and references on the subject. There is a useful section on using the operating microscope and on preliminary suturing exercises involving animal vessels, nerves and tubes. The descriptions are excellent and the manual promises to become a necessary adjunct to any anastomosis workshop involved in microsurgical techniques

M. C. Pietroni

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Erratum

'*Acute pancreatitis*' reviewed by M. Trede, *Br J Surg* 1988, **75**: 1151, right hand column, lines 38–40: for '**Acute pancreatitis**, *G. Glazer, 180 × 238 mm. Pp. 440. Illustrated. 1988. London· Baillière Tindall. £35.00*' read '**Acute Pancreatitis**, *G. Glazer and J. H. C. Ranson. 160 × 240 mm. Pp 456. Illustrated. 1988 London. Baillière Tindall. £35.00*'. We apologize for this error.

Notices and announcements

5–6 January 1989
69th Meeting of the Surgical Research Society
Canterbury, UK
Information Hilary Thompson, The London Hospital, London E1 1BB, UK

21–22 January 1989
Hong Kong Surgical Forum
University of Hong Kong, Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

25–26 January 1989
Thrombolysis: The Dawn of a New Era?
U.K.
Information. Penny Robinson, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

12–18 February 1989
Diabetic Control and Complications: An Interactive Workshop
London, UK
Information: Director, Courses Department, 65 Davies Street, London W1Y 2AA

19–22 February 1989
3rd United Arab Emirates Cancer Conference
Dubai, United Arab Emirates
Information Conference Secretariat, 3rd U A E. Cancer Conference, Emirates Medical Association, P.O. Box 6600, Dubai, United Arab Emirates

19–23 February 1989
7th Congress of the Association of Surgeons of South East Asia
Penang, Malaysia
Information. Congress Secretariat, 7th Congress Ssian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

19–24 February 1989
Diagnostic Imaging Update
Park City, Utah, USA
Information Radiology Postgraduate Education, Room C324, University of California, San Francisco, California 94143-0628, USA

25–26 February 1989
Second Annual Congress on the North American Society of Phlebology
New Orleans, USA
Information. Pat Curl, Course Coordinator, North American Society of Phlebology, 3960 Park Boulevard, Suite E, San Diego, California 92103, USA

4–11 March 1989
7th Winter Congress: Diagnostic Imaging
Courchevelle, France
Information· Ms Mary Ullman, Winter Congress, 21915 Roscoe Boulevard, Suite 222, Canoga Park, California 91304, USA

5–7 March 1989
Surgical Masterclass for Consultants and Senior Registrars in General Surgery
Aviemore, U.K.
Information Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

5–10 March 1989
Magnetic Resonance Imaging Update 1989: Winter Conference
Snowbird, Utah, USA
Information. Radiology Postgraduate Education, Room C324, University of California, San Francisco, California 94143-0628, USA

12–15 March 1989
Current Problems in Breast Cancer
Vienna, Austria
Information· Secretariat ICS, Elisabeth Ribar-Maurer, c/o Wiener Medizinische Akademie, Alser Strasse 4, A 1090 Vienna, Austria

29–31 March 1989
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information· The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–9 April 1989
4th ASEAN Otorhinolaryngological Head and Neck Congress
Singapore
Information Dr R. E Stanley, Organizing Secretary, c/o ENT Department, Singapore General Hospital, Singapore 0316

12–14 April 1989
VIth International Conference: Polymers in Medicine and Surgery
Leeuwenhorst Congress Centre, The Netherlands
Information· Joanna Evans-Thomas, Conference Officer, The Plastics and Rubber Institute, 11 Hobart Place, London SW1W 0HL, UK

21–23 June 1989
71st Annual Meeting of The Endocrine Society
Seattle, Washington, USA
Information The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–27 June 1989, 28–30 June 1989
Second Mediterranean Surgical Congress
Athens, and continued in Heraklion, Crete, Greece
Information: Ms Peggy Alexopoulou, Public Relations Centre, 56 Hippocratous Street, 106 80 Athens, Greece

2–15 July 1989
Neonatal and Paediatric Surgery
Manchester, UK
Information. Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

15–16 July 1989
Hong Kong Surgical Forum
Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information. International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

28–30 August 1989
International Conference on Blood-borne Infections in the Workplace
Stockholm, Sweden
Information Ms Catharina Ostrom, Congrex AB, PO Box 5619, S-114 86 Stockholm, Sweden

6 September 1989
2nd Meeting of the Working Group Paediatric Surgical Research; Kinderchirurgische Forschung
Graz, Austria
Information Professor Dr H Sauer, Department of Paediatric Surgery, University of Graz, Heinrichstrasse 31, A-8010 Graz, Austria

6–8 September 1989
Fourth World Congress of the International Society for Diseases of the Oesophagus
Chicago, Illinois, USA
Information: 4th World Congress of the International Society of Diseases of the Oesophagus, 911 Busse Highway, Park Ridge, Illinois 60068, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information International Congress and Convention Association, P.O Box 50006, Tel Aviv 61500, Israel

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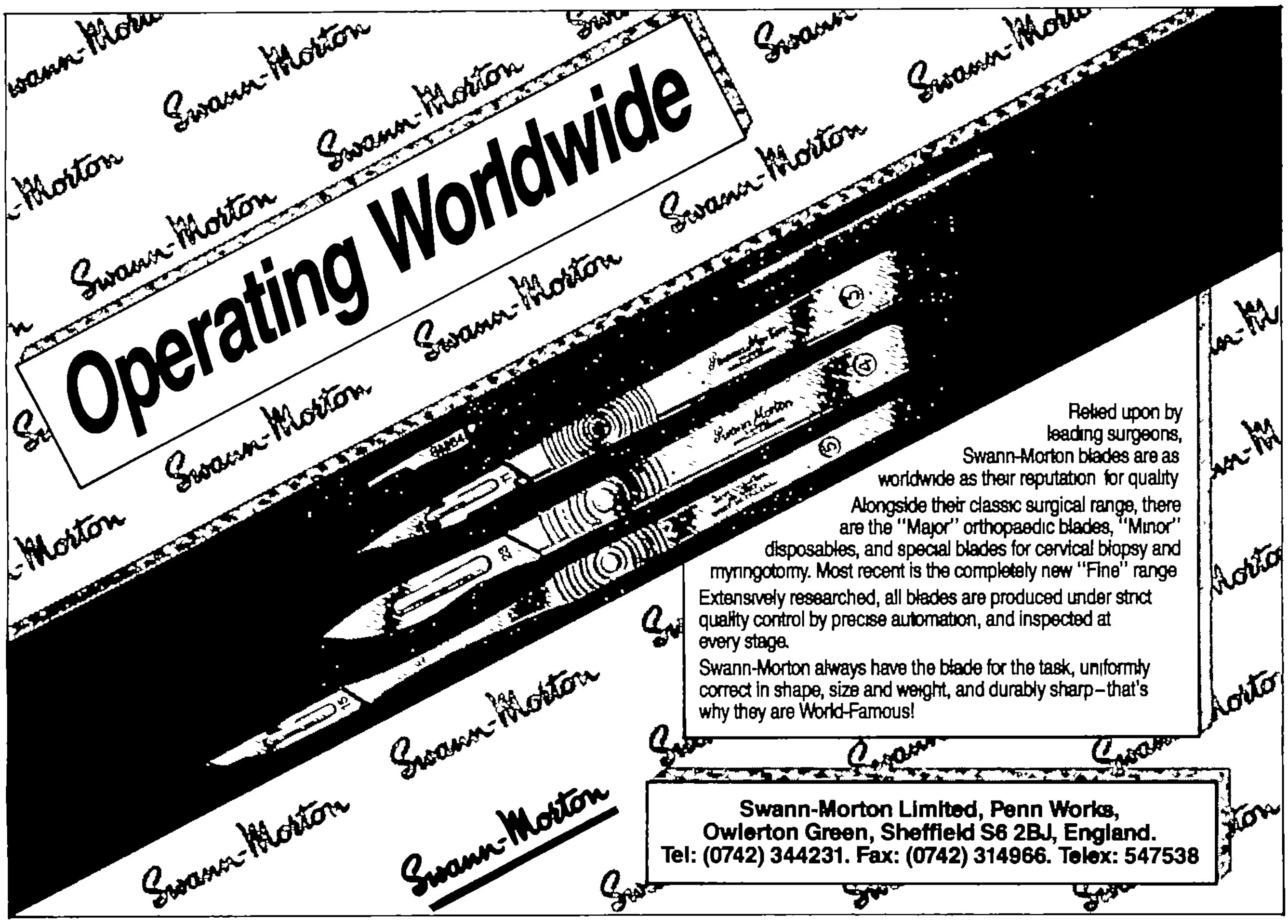

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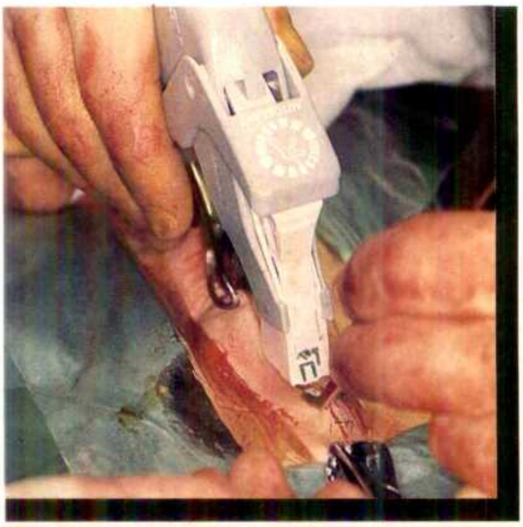
The 'Precise' skin stapling system



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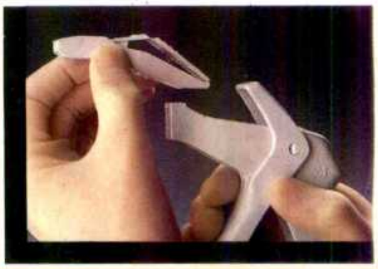

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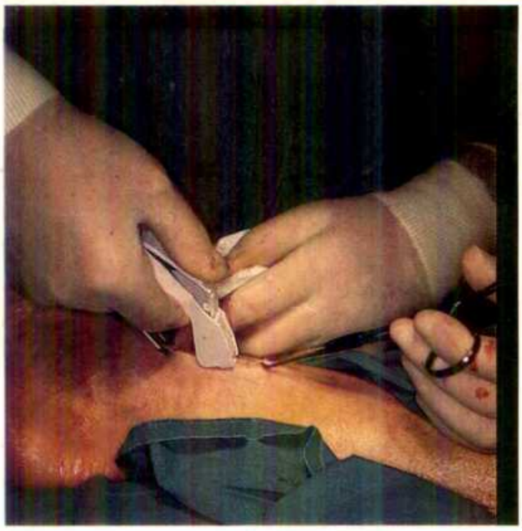

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